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P-3487

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

Re: Expediente No. 12-154.938

Solicitud de patente a nombre de **UNIVERSITY OF SOUTHERN CALIFORNIA**

Yo, SILVANA MARIA LOPEZ DIAZ identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **UNIVERSITY OF SOUTHERN CALIFORNIA**, solicitante de la patente de la referencia, interpongo recurso de reposición contra la resolución No. 2743 del día 30 de enero de 2015, expedida por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente para la solicitud contenida en el expediente de la referencia

1. FUNDAMENTOS DEL RECURSO**1.1 Actos administrativos previos**

En primer lugar, mi mandante se permite manifestar a ese despacho que se reafirma en todos y cada uno de los argumentos que hacen parte integrante de la respuesta al oficio de fondo No. 6333 notificado por fijación en lista el 03 de junio de 2014, presentada ante ese despacho el 25 de septiembre de 2014.

1.2 El análisis del nivel inventivo

Ahora bien, como se evidenciará a continuación, es deseo del solicitante presentar argumentos contra las declaraciones de ese Despacho a partir de las cuales el examinador establece que las reivindicaciones 1 a 8 carecen de nivel inventivo a la luz de los documentos D1, D2 y D3.

En primer lugar, volvemos sobre el particular que el artículo 18 de la Decisión 486 establece que "*Se considerará que una invención tiene nivel inventivo,*

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si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.

A este respecto, el solicitante desea manifestar en primer lugar que el documento D3 describe una formulación tópica para factor de crecimiento de fibroblasto ácido (aFGF), una proteína 15.9 kDa, en la cura de heridas de grosor completo, donde la formulación consiste de una solución de aFGF y heparina en 1% d hidroxietil celulosa (HEC) en salida amortiguada con fosfato (PBS).

Del mismo modo, dicha anterioridad D3 indica que el único propósito de incluir HEC es para mejorar la viscosidad, tal como se establece en la página 68, segundo párrafo, donde se indica que *“El agente mejorador de viscosidad, HEC, se incorporó en la formulación aFGF para prevenir o minimizar la finalización de la dosis aplicada desde el sitio de la herida”*. Los experimentos ilustrados en la figura 3 muestran que el efecto de la formulación en la curación de la herida es el mismo bien sea que el HEC esté presente o no (página 68, segundo párrafo completo y la figura 3).

De acuerdo con lo anterior, queda claro para un experto en la materia que no existe ninguna enseñanza en este documento D3 que sugiera que las formulaciones tópicas que contienen HEC se pueden utilizar para terapéuticos péptidos pequeños, o que la presencia de HEC tiene un efecto positivo en la cinética de la liberación del fármaco.

Capítulo de libro con hipervínculo

Ahora bien, el solicitante manifiesta que el capítulo 1 del Manual de Tecnología Farmacéutica de Liberación Controlada presenta un artículo escrito por Rodríguez y otros, titulado “Derivados Hidrófilos de Celulosa como Portadores de Entrega de Fármacos” (relacionado acá como “Rodríguez”). Rodríguez discute el uso de polímeros de base celulosa comprimidos, que incluyen hidroxietil celulosa (HEC), como una matriz para la liberación de fármaco en formulaciones orales (es decir, tabletas) para terapias de moléculas pequeñas (por ejemplo, se utilizó fenilpropanolamina como el fármaco modelo).

En contraste, la invención actualmente reivindicada describe el uso de HEC en preparaciones de gel para formulaciones tópicas de Nle3 A(1-7), los cuales son terapias de péptidos con por lo menos 5 aminoácidos.

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Para diferentes rutas de administración, la liberación del fármaco depende directamente de las diferentes propiedades del fármaco así como de la matriz de polímero. Así, para administración oral, la liberación del fármaco depende de la tasa de difusión del fármaco y el desgaste de la matriz de polímero, también referenciado como erosión (Rodríguez, página 1, segundo párrafo). En contraste, la liberación de un fármaco a partir de una formulación tópica en gel típicamente depende de la penetración del fármaco del gel en la herida o a través de la superficie de la piel.

Así, para las formulaciones orales descritas en Rodríguez, los polímeros de base celulosa se administran en una forma comprimida, en la forma de una tableta. Con la administración, los fluidos gástricos son capaces de penetrar la superficie de la tableta, la cual se hincha y forma una capa externa de gel. El fármaco es capaz de difundirse a partir de esta capa de gel, la cual también experimenta erosión en su superficie externa. A medida que la superficie de gel erosiona, los fluidos penetran más profundo en el centro de la tableta, expandiendo la capa de gel más profundo dentro de la tableta. Idealmente, la tasa de erosión debe ser paralela a la tasa de penetración de solvente, manteniendo el grosor de la capa de gel constante a lo largo de todo el proceso de disolución de la tableta. Se notó entonces que para obtener una tasa constante de liberación de fármaco, la penetración del solvente (y la erosión de polímero) debe ser mucho más lenta que la difusión del fármaco (Rodríguez, página 1, segundo párrafo). Con esto en mente, Rodríguez probó las propiedades de liberación de fármaco de fenilpropanolamina en varias matrices de polímero basado en celulosa.

De este modo, los estudios de liberación de fármaco revelaron que las diferencias en la tasa de liberación del fármaco no se pronunciaron entre los diferentes polímeros (figura 6, página 13).

Así, de los polímeros basados en celulosa probados por Rodríguez y otros, se encontró que HEC fue el más hidrófilo (Tabla 2, página 6) y mostró tasas de disolución de polímero mucho mayor (es decir, erosión) que cualquier otro tipo de polímero probado cuando se ubicó en un medio de disolución (Figura 5). Esto no es ideal para administración oral, dado que las matrices de polímero que se someten a tasas de erosión más lentas se han encontrado que alcanzan tasas de liberación de fármaco más constantes. En general, Rodríguez identificó hidroxipropilmetilcelulosa (HPMC), la cual tuvo tasa de erosión de polímero mucho menores, como el polímero de

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base celulosa ideal para ser usado en formulaciones de fármacos orales.

Así las cosas, Rodríguez se aleja del uso de HEC, ya que el HEC sería menos adecuado para las formulaciones orales descritas allí en comparación con otros polímeros de base celulosa probados. De este modo, no existe ninguna sugerencia en Rodríguez sobre que las propiedades no adecuadas para las formulaciones orales serían de alguna manera deseables para formulaciones tópicas. Además, dado que la capa de gel se ubica sobre la parte superior de la piel y no experimenta erosión en una formulación tópica, las enseñanzas relacionadas con las características de erosión en el contexto oral no son relevantes para la materia objeto de las presentes reivindicaciones.

Sumado a lo anterior, el solicitante desea indicar que Rodríguez no menciona el uso de polímeros de base celulosa en alguna formulación de fármaco tópica, mucho menos en formulaciones que específicamente contienen terapia de péptido. Además, no se encontró que el HEC presente alguna propiedad de liberación de fármaco significativamente diferente en comparación con otros polímeros de base celulosa probados (figura 3, página 13). La única propiedad que separa el HEC de otros polímeros es la rápida tasa de disolución o erosión del polímero, la cual no es relevante para las formulaciones tópicas de la presente invención, y la cual fue indicada como indeseable en el contexto de las formulaciones orales. También se debe notar que Rodríguez no menciona carboximetil celulosa (CMC), y por lo tanto no existe ninguna comparación directa entre HEC y CMC.

De acuerdo con lo anterior, queda claro que la materia objeto definida en las reivindicaciones 1 a 8 presenta un efecto técnico sorprendente e inesperado con relación al estado del arte, con lo cual se puede indicar que no hubiera sido obvia para un experto en la materia partiendo de los documentos D1, D2 y/o D3, cumpliendo así con el requisito de nivel inventivo tal como se encuentra definido en el artículo 18 de la Decisión 486, principalmente teniendo en cuenta el hecho que lo mencionado en el documento D3, que es el que de acuerdo con el análisis del examinador se combina con el fin de obtener de forma obvia la presente invención, no es adecuado para formulaciones tópicas y las tasas de liberación de fármaco, tal como se demostró anteriormente.

En resumen, me permito establecer nuevamente que debido a los argumentos expuestos anteriormente y los radicados ante esa Superintendencia el 25 de septiembre de 2014, la presente solicitud cumple

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cabalmente con los requisitos de patentabilidad respecto a la formulación expuesta en las reivindicaciones 1 a 8.

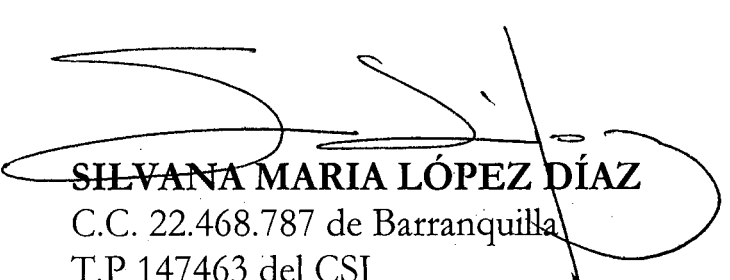
Finalmente y sin apartarse del conocimiento de la independencia entre oficinas de propiedad intelectual deseo del solicitante informar que las patentes correspondientes de Estados Unidos, Europa y Japón de las cuales se adjuntan los reportes y reivindicaciones aceptadas. Es importante poner de manifiesto que los argumentos expuestos para estos tres casos en cuanto a los resultados inesperados en la liberación del péptido desde la formulación polimérica, fueron suficientes para superar las objeciones planteadas por las diversas oficinas.

2. Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

a) Que de conformidad con lo previsto por los artículos 3, 42 y 80 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo se consideren y se resuelvan TODOS los argumentos y TODAS las cuestiones planteadas así como las que aparezcan con motivo de este recurso.

b) Que se revoque la resolución **No. 2743 emitida el 30 de enero de 2015** por el Superintendente de Industria y Comercio, y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante.

Señor Superintendente,



SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787 de Barranquilla

T.P 147463 del CSJ

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ANEXO 1

Copia de reportes y reivindicaciones aceptadas de las patentes correspondientes de Estados Unidos, Europa y Japón.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

20306 7590 05/02/2012
MCDONNELL BOEHNNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER

ROMEIO, DAVID S

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 05/02/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/364,061	02/01/2012	Kathleen E. Rodgers	11-1000-US	8388

TITLE OF INVENTION: METHODS FOR TREATING DIABETIC FOOT ULCERS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	\$870	\$0	\$0	\$870	08/02/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.
- B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

- A. Pay TOTAL FEE(S) DUE shown above, or
- B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

7

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

20306 7590 05/02/2012
MCDONNELL BOEHNNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/364,061	02/01/2012	Kathleen E. Rodgers	11-1000-US	8388

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APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	\$870	\$0	\$0	\$870	08/02/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROMEO, DAVID S	1647	514-928000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a **Customer Number is required.**

2. For printing on the patent front page, list

- (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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CHICAGO, IL 60606		

EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/02/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

9

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/364,061	RODGERS ET AL.	
	Examiner	Art Unit	
	DAVID ROMEO	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to April 6, 2012.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 1-7,9-11 and 19-32.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
 6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date ____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
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| <ol style="list-style-type: none"> 1. ☐ Notice of References Cited (PTO-892) 2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 3. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date <u>0412,0412</u> 4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material | <ol style="list-style-type: none"> 5. ☐ Notice of Informal Patent Application 6. ☒ Interview Summary (PTO-413),
Paper No./Mail Date ____. 7. ☒ Examiner's Amendment/Comment 8. ☒ Examiner's Statement of Reasons for Allowance 9. ☐ Other ____. |
|---|--|

/David S Romeo/
Primary Examiner, Art Unit 1647

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be

5 submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with David Harper on 04/25/2012.

The application has been amended as follows:

IN THE CLAIMS:

- 10 1. A method for treating diabetic foot ulcers, comprising administering to a human patient suffering from a diabetic foot ulcer an amount of a peptide of at least 5 contiguous amino acids of Nle3 A(1-7) effective to treat the diabetic foot ulcer, wherein the peptide is administered topically in a gel formulation that comprises about 0.5% to about 4% hydroxyethyl cellulose (HEC) on a weight (mg)/volume (ml) basis, or on a
15 weight/weight (mg) basis.

2. The method of claim 1, wherein the peptide comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO: 1).

- 20 3. The method of claim 1, wherein the peptide consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO: 1).

Art Unit: 1647

4. The method of claim 1, wherein the diabetic foot ulcer is one caused, at least in part, by neuropathy and resulting pressure.

5. The method of claim 1, wherein the diabetic foot ulcer comprises one or more
5 calluses.

6. The method of claim 1, wherein the diabetic foot ulcer is a chronic ulcer.

7. The method of claim 6, wherein the chronic foot ulcer has not responded to any
10 other treatment.

8. (Cancelled)

9. The method of claim ~~8~~1, wherein the peptide is administered as a topical
15 formulation forming a continuous film covering the entire area of the diabetic ulcer.

10. The method of claim ~~8~~1, wherein the peptide is administered in a hydrogel formulation.

20 11. The method of claim 1, wherein the peptide is administered at a concentration of about 0.03 % to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

14

12. – .18 (Cancelled)

19. The method of claim 2, wherein the diabetic foot ulcer is one caused, at least in
5 part, by neuropathy and resulting pressure.

20. The method of claim 2, wherein the diabetic foot ulcer comprises one or more
calluses.

10 21. The method of claim 2, wherein the diabetic foot ulcer is a chronic ulcer.

22. The method of claim 21, wherein the chronic foot ulcer has not responded to any
other treatment.

15 23. The method of claim 2, wherein the peptide is administered as a topical
formulation forming a continuous film covering the entire area of the diabetic ulcer.

24. The method of claim 2, wherein the peptide is administered in a hydrogel
formulation.

Art Unit: 1647

25. The method of claim 2, wherein the peptide is administered at a concentration of about 0.03 % to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

5 26. The method of claim 3, wherein the diabetic foot ulcer is one caused, at least in part, by neuropathy and resulting pressure.

27. The method of claim 3, wherein the diabetic foot ulcer comprises one or more calluses.

10

28. The method of claim 3, wherein the diabetic foot ulcer is a chronic ulcer.

29. The method of claim 28, wherein the chronic foot ulcer has not responded to any other treatment.

15

30. The method of claim 3, wherein the peptide is administered as a topical formulation forming a continuous film covering the entire area of the diabetic ulcer.

31. The method of claim 3, wherein the peptide is administered in a hydrogel

20 formulation.

32. The method of claim 3, wherein the peptide is administered at a concentration of about 0.03 % to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

5 The following is an examiner's statement of reasons for allowance:

Rodgers (J Pept Res. 2005 Dec;66 Suppl 1:41-7) is the closest prior art of record. Rodgers teaches that daily application of fragments of Nle3-A(1-7) of five or six amino acids accelerated healing in two models of dermal injury (Abstract). The viscous vehicle was prepared from carboxymethyl cellulose (CMC) consisting of 10% low
10 viscosity CMC followed by mixing with peptide solutions (page 42, right column, penultimate paragraph). Nle3 A(1-7) is being developed as a therapeutic for the treatment of dermal wounds, including diabetic ulcers and scar reduction (page 46, left column, last paragraph). However, Rodgers does not teach a gel formulation that comprises about 0.5% to about 4% hydroxyethyl cellulose (HEC) on a weight
15 (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

According to the specification,

20 These formulations comprising low percentage HEC [hydroxyethyl cellulose] (ie: 2%) matrices provided a 10-fold increase in peptide release over a 24 hour period from formulations such as those comprising 10% carboxymethyl cellulose (CMC), a result that would be unexpected to those of skill in the art. Furthermore, the data show that the HEC matrices are more biocompatible than HPMC and CMC formulations tested. (page 6, lines 7-11)

25 See also page 8, lines 19-27. These properties of low percentage HEC formulations comprising Nle3 A(1-7) are not taught by the prior art of record. The

17

Art Unit: 1647

specification's evidence of unobvious or unexpected advantageous properties of these formulations comprising low percentage HEC matrices are enough to rebut prima facie obviousness.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, RAM SHUKLA, CAN BE REACHED AT (571) 272-0735.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-0835.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE [HTTP://PAIR-DIRECT.USPTO.GOV](http://PAIR-DIRECT.USPTO.GOV). CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
APRIL 29, 2012

18

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		13364061
	Filing Date		2012-02-01
	First Named Inventor	Rodgers, et al.	
	Art Unit	1647	
	Examiner Name	Romeo, David S.	
	Attorney Docket Number	11-1000-US	

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	Attorney Docket Number	11-1000-US	

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	Attorney Docket Number	11-1000-US		

	6	2001/44270	WO		2001-06-21	DiZerega, et al.		☐
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27



US008207234B1

(12) **United States Patent**
Rodgers et al.(10) **Patent No.:** **US 8,207,234 B1**
(45) **Date of Patent:** **Jun. 26, 2012**(54) **METHODS FOR TREATING DIABETIC FOOT ULCERS**(75) Inventors: **Kathleen E. Rodgers**, Long Beach, CA (US); **Gere S. diZerega**, San Luis Obispo, CA (US)(73) Assignee: **University of Southern California**, Los Angeles, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/441,653**(22) Filed: **Apr. 6, 2012****Related U.S. Application Data**

(62) Division of application No. 13/364,061, filed on Feb. 1, 2012.

(60) Provisional application No. 61/438,780, filed on Feb. 2, 2011.

(51) **Int. Cl.****A61K 38/08** (2006.01)
A61K 47/38 (2006.01)
C07K 7/14 (2006.01)
C07K 17/04 (2006.01)
C07K 17/12 (2006.01)(52) **U.S. Cl.** **514/928; 424/488; 530/316; 930/40**(58) **Field of Classification Search** None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**5,015,629 A 5/1991 DiZerega et al.
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Primary Examiner — David Romeo(74) *Attorney, Agent, or Firm* — McDonnell Boehnen Hulbert & Berghoff LLP(57) **ABSTRACT**

The present invention provides methods and pharmaceutical formulations for treating diabetic foot ulcers.

12 Claims, 3 Drawing Sheets

28



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(12) **United States Patent**
Rodgers et al.

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(45) Date of Patent: ***Sep. 17, 2013**

(54) **METHODS FOR TREATING DIABETIC FOOT ULCERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(51) **Int. Cl.**

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C07K 7/14 (2006.01)

C07K 17/04 (2006.01)

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(52) **U.S. Cl.**

USPC **514/928**; 424/488; 530/316; 930/40

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — David Romeo

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(57) **ABSTRACT**

The present invention provides methods and pharmaceutical formulations for treating diabetic foot ulcers.

27 Claims, 3 Drawing Sheets

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Figure 1

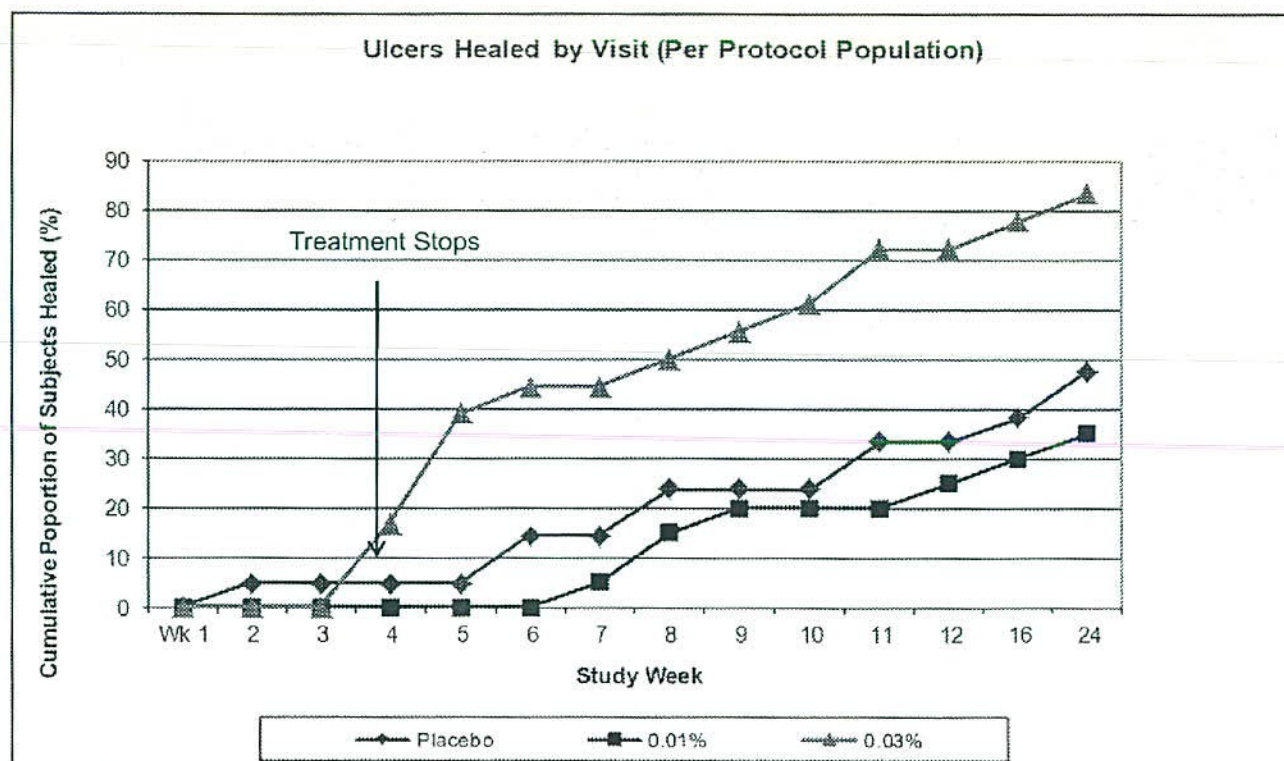
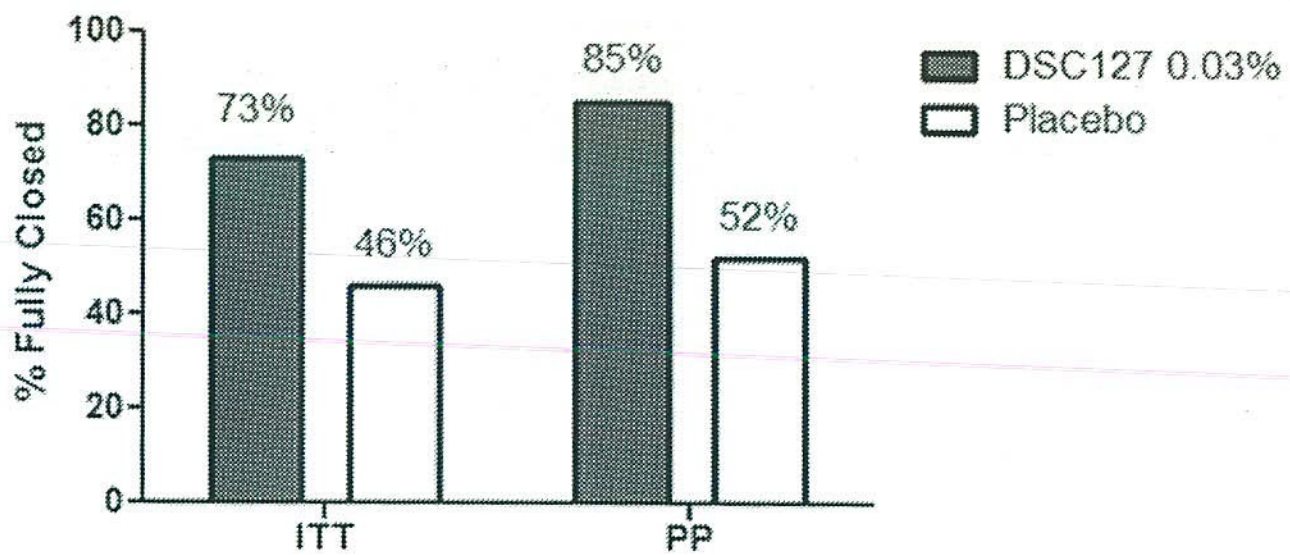
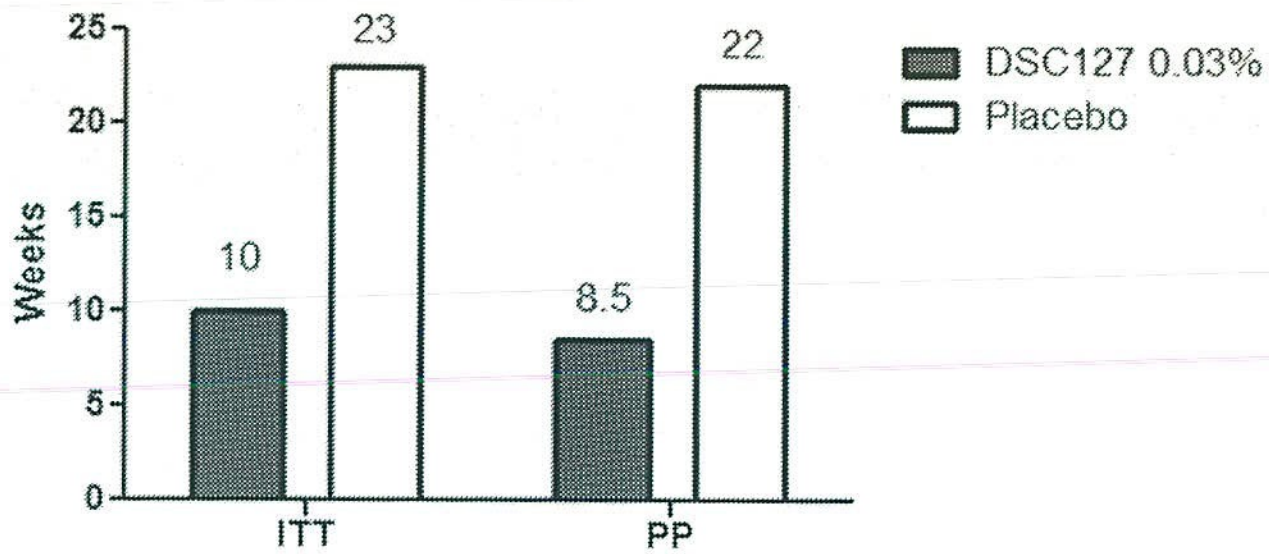


Figure 2



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Figure 3



1

METHODS FOR TREATING DIABETIC FOOT ULCERS

CROSS REFERENCE

This application is a continuation of U.S. application Ser. No. 13/364,061 filed Feb. 1, 2012 which claims priority to U.S. Provisional Patent Application Ser. No. 61/438,780 filed Feb. 2, 2011, incorporated by reference herein in their entirety.

BACKGROUND

Diabetes is common, disabling and deadly. In the U.S., diabetes has reached epidemic proportions. According to the American Diabetes Association, about 24 million people (8% of the total U.S. population) have diabetes, and nearly two million new cases are diagnosed in people aged 20 years or older each year. If current trends continue, 1 in 3 Americans will develop diabetes at some point in their lifetime, and those with diabetes will lose, on average, 10-15 years of life expectancy. Importantly, up to 25% of people with diabetes will develop a diabetic foot ulcer, resulting in 3 million diabetic foot ulcers annually in the U.S. alone. More than half of all foot ulcers will become infected, thus requiring hospitalization, and 1 in 5 will require an amputation that carries a high risk of mortality.

Without question, diabetes puts tremendous economic pressure on the U.S. healthcare system. Total costs (direct and indirect) of diabetes have reached \$174 billion annually, and people with diagnosed diabetes have medical expenditures that are over two times higher than medical expenditures for people without diabetes. Hospitalization costs alone are \$16,000 to \$20,000 for a patient with a diabetic foot ulcer, and direct and indirect costs of an amputation range from \$20,000 to \$60,000 per patient. A recent study by researchers at the University of Chicago suggested that treatment costs for diabetes in the United States would reach \$336 billion by the year 2034. Advanced, cost-effective treatment modalities for diabetes and its co-morbidities, including diabetic foot ulcers, are in great need, yet in short supply, globally. According to the American Diabetes Association, by the year 2025 the prevalence of diabetes is expected to rise by 72% to 324 million people worldwide.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides methods for treating diabetic foot ulcers, comprising administering to a human patient suffering from a diabetic foot ulcer an amount of a peptide of at least 5 contiguous amino acids of Nle3 A(1-7), or salt thereof, effective to treat the diabetic foot ulcer. In one embodiment, the peptide comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salt thereof. In another embodiment, the peptide consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salt thereof. In various embodiments, the diabetic foot ulcer is one caused, at least in part, by neuropathy and resulting pressure; the diabetic foot ulcer comprises one or more calluses; and the diabetic foot ulcer is a chronic ulcer. In a further embodiment, the chronic foot ulcer has not responded to any other treatment.

In another embodiment, the peptide is administered topically. In a further embodiment, the peptide is administered as a topical formulation forming a continuous film covering the entire area of the diabetic ulcer. In a still further embodiment, the peptide is administered in a hydrogel formulation. In another embodiment, the peptide is administered at a concen-

2

tration of about 0.03% to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In a further embodiment, the peptide is administered in a gel formulation that about 0.5% to about 4% hydroxyethyl cellulose (HEC) on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

All embodiments of the first aspect of the invention can be combined unless the context dictates otherwise.

In a second aspect, the present invention provides pharmaceutical formulations, comprising:

(a) about 0.5% to about 4% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis; and

(b) a peptide of at least 5 contiguous amino acids of Nle3 A(1-7), or salt thereof;

wherein the peptide is present at a concentration of about 0.03% to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

In one embodiment, the peptide comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salt thereof. In another embodiment, the peptide consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salt thereof. In a further embodiment, the pharmaceutical formulation comprises about 1% to about 3% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In a still further embodiment, the pharmaceutical formulation comprises about 2% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In another embodiment, the formulation comprises a hydrogel formulation. All embodiments of the second aspect of the invention can be combined unless the context dictates otherwise.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph showing the ulcers healed by visit in the Per Protocol (PP) patient population taking NorLeu³-A(1-7).

FIG. 2 is a graph showing the percentage of fully healed ulcers (100% wound closure) in the patient population taking NorLeu³-A(1-7) (also referred to as "DSC127").

FIG. 3 is a graph showing the median time to fully healed ulcers (100% wound closure) in the patient population taking NorLeu³-A(1-7) (also referred to as "DSC127").

DETAILED DESCRIPTION OF THE INVENTION

All references cited are herein incorporated by reference in their entirety. Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991, Academic Press, San Diego, Calif.), "Guide to Protein Purification" in *Methods in Enzymology* (M. P. Deutscher, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990, Academic Press, San Diego, Calif.), *Culture of Animal Cells: A Manual of Basic Technique*, 2nd Ed. (R. I. Freshney. 1987, Liss, Inc. New York, N.Y.), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E. J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, Tex.).

As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. "And" as used herein is interchangeably used with "or" unless expressly stated otherwise.

All embodiments of any aspect of the invention can be used in combination, unless the context clearly dictates otherwise.

34

In a first aspect, the present invention provides methods for treating diabetic foot ulcers, comprising administering to a human patient suffering from a diabetic foot ulcer an amount of a peptide of at least 5 contiguous amino acids of Nle3 A(1-7), or salt thereof, effective to treat the diabetic foot ulcer.

As demonstrated in the examples that follow, the inventors have demonstrated that the methods of the invention can be used to treat diabetic foot ulcers, and provide substantial improvement over standard therapies.

Nle3A(1-7) (or NorLeu³-A(1-7); also referred to as "DSC127") is a peptide consisting of the amino acid sequence Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1). In various embodiments, the peptide administered to the human patient may comprise or consist of Asp-Arg-Nle-Tyr-Ile (SEQ ID NO:2), Asp-Arg-Nle-Tyr-Ile-His (SEQ ID NO:3), or most preferably Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salts thereof. Nle3A(1-7) or salts thereof may be chemically synthesized or recombinantly expressed, each of which can be accomplished using standard methods in the art.

In one embodiment, the peptide, or salt thereof, is administered at a concentration of about 0.03% to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In various further embodiments, the peptide, or salt thereof, is administered at a concentration of about 0.03% to about 0.75%; about 0.03% to about 0.5%; about 0.03% to about 0.25%; about 0.03% to about 0.1%; about 0.03% to about 0.075%; about 0.03% to about 0.05%; and about 0.03%; all on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

The human patient may be suffering from Type I diabetes or Type II diabetes, and has a foot ulcer, defined as an open wound anywhere on the foot (heel, mid-foot, and forefoot).

As used herein, "treating" a diabetic foot ulcer includes

(a) limiting the progression in size, area, and/or depth of the foot ulcer;

(b) reducing size, area, and/or depth of the foot ulcer;

(c) increasing rate of healing and/or reducing time to healing;

(d) healing of the foot ulcer (100% epithelialization with no drainage); and

(e) decreased incidence of amputation or slowing in time to amputation.

The foot ulcer may be caused by any underlying pathology, including but not limited to neuropathy, trauma, deformity, high plantar pressures, callus formation, edema, and peripheral arterial disease. In preferred embodiments, the human diabetic foot ulcer is one caused, at least in part, by neuropathy and resulting pressure (weight bearing on the extremity due to lack of feeling in the foot). As is known to those of skill in the art, human diabetic foot ulcers tend to be due to neuropathy and pressure, which differs significantly from, for example, murine acute wounds. In a further preferred embodiment, the diabetic foot ulcer comprises one or more calluses.

In a further embodiment, the diabetic foot ulcer is a chronic ulcer. As used herein, a "chronic" foot ulcer is one that has been present for at least 7 days with no reduction in size; preferably at least 14 days; even more preferably, present at least 21 or 28 days with no reduction in size. In a further preferred embodiment that can be combined with any of these embodiments, the chronic foot ulcer has not responded (ie: no reduction in size, area, and/or depth of the foot ulcer; no healing of the foot ulcer) to any other treatment.

The peptide or salt thereof may be administered by any suitable route, preferably via topical administration. In one embodiment, the methods of the invention can comprise administering a topical formulation as often as deemed

appropriate, ie: once per day, twice per day, etc. The methods may further comprise administration of the peptide, or salt thereof for as longed as deemed desirable by an attending physician, for example, until healing of the ulcer. For administration, it is preferred that the topical formulation form a continuous film covering the entire area of the ulcer, including the margins. In a preferred embodiment, the topical formulation is applied with a thickness of approximately 0.25 to 2 mm; preferably 0.5 to 1.5 mm; preferably about 1 mm in thickness.

In one embodiment, the topical administration comprises administration in a formulation selected from the group consisting of hydrogels, creams, ointments, pastes, and lotions. The formulations may be applied in any suitable manner, which may include any wound dressings to seal in the formulation deemed appropriate by the human patient or caregiver. Exemplary such dressings, include, but are not limited to, semipermeable films, foams, hydrocolloids, and calcium alginate swabs.

The methods may further comprise debridement in and around the wound in combination with administration of the peptide and formulations thereof. Debridement of all necrotic, callus, and fibrous tissue is typically carried for treatment of diabetic foot ulcers. Unhealthy tissue is sharply debrided back to bleeding tissue to allow full visualization of the extent of the ulcer and to detect underlying abscesses or sinuses. Any suitable debridement technique can be used, as determined by an attending physician. The wound can then be thoroughly flushed with sterile saline or a non-cytotoxic cleanser following debridement.

In another embodiment, the topical formulation comprises about 0.5% to about 4% hydroxyethyl cellulose (HEC) on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In various further embodiments, the topical formulation may comprise about 1% to about 3% HEC, or about 2% HEC, on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. These formulations comprising low percentage HEC (ie: 2%) matrices provided a 10-fold increase in peptide release over a 24 hour period from formulations such as those comprising 10% carboxymethylcellulose (CMC), a result that would be unexpected to those of skill in the art. Furthermore, the data show that the HEC matrices are more biocompatible than HPMC and CMC formulations tested.

The peptides, or salt thereof may be administered together with one or more (a) a lyoprotectant; (b) a surfactant; (c) a bulking agent; (d) a tonicity adjusting agent; (e) a stabilizer; (f) a preservative and/or (g) a buffer. In some embodiments, the buffer in the pharmaceutical composition is a Tris buffer, a histidine buffer, a phosphate buffer, a citrate buffer or an acetate buffer. The peptides may be administered with a lyoprotectant, e.g. sucrose, sorbitol or trehalose. In certain embodiments, the peptides may be administered with a preservative e.g. benzalkonium chloride, benzethonium, chlorhexidine, phenol, m-cresol, benzyl alcohol, methylparaben, propylparaben, chlorobutanol, o-cresol, p-cresol, chlorocresol, phenylmercuric nitrate, thimerosal, benzoic acid, and various mixtures thereof. In other embodiments, the peptides may be administered with a bulking agent, like glycine. In yet other embodiments, the peptides may be administered with a surfactant e.g., polysorbate-20, polysorbate-40, polysorbate-60, polysorbate-65, polysorbate-80 polysorbate-85, poloxamer-188, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan trilaurate, sorbitan tristearate, sorbitan trioleate, or a combination thereof. The peptides may be administered with a tonicity adjusting agent, e.g., a compound that renders the formulation substantially isotonic or isoosmotic with human blood.

5

Exemplary tonicity adjusting agents include sucrose, sorbitol, glycine, methionine, mannitol, dextrose, inositol, sodium chloride, arginine and arginine hydrochloride. In other embodiments, the peptides may be administered with a stabilizer, e.g., a molecule which, when combined with the peptide substantially prevents or reduces chemical and/or physical instability of the protein of interest in lyophilized or liquid form. Exemplary stabilizers include sucrose, sorbitol, glycine, inositol, sodium chloride, methionine, arginine, and arginine hydrochloride, paraben, and combinations of methyl paraben and propyl paraben.

In all aspects and embodiments of the invention, suitable acids which are capable of forming salts with the peptides include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, phosphoric acid and the like; and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, anthranilic acid, cinnamic acid, naphthalene sulfonic acid, sulfanilic acid and the like. Suitable bases capable of forming salts with the peptides include, but are not limited to, inorganic bases such as sodium hydroxide, ammonium hydroxide, potassium hydroxide and the like; and organic bases such as mono-, di- and tri-alkyl and aryl amines (e.g., triethylamine, diisopropyl amine, methyl amine, dimethyl amine and the like) and optionally substituted ethanol-amines (e.g., ethanolamine, diethanolamine and the like).

The peptides or salts thereof can further be derivatized to provide enhanced half-life, for example, by linking to polyethylene glycol. The peptides or salts thereof may comprise L-amino acids, D-amino acids (which are resistant to L-amino acid-specific proteases *in vivo*), a combination of D- and L-amino acids, and various "designer" amino acids (e.g., β -methyl amino acids, α -methyl amino acids, and $N\alpha$ -methyl amino acids, etc.) to convey special properties.

The polypeptides may be the sole active agent in the pharmaceutical composition, or the composition may further comprise one or more other active agents suitable treating diabetic foot ulcers, such as antibiotics. The methods may be used in conjunction with other foot ulcer therapies, including but not limited to negative pressure wound therapy, total contact casts, removable cast walkers, half-shoes, becaplermin, infection control, and hyperbaric oxygen therapy.

The methods may include any other embodiments as disclosed in the example that follows. Such embodiments may be used in any combination in the methods of the invention, unless the context clearly dictates otherwise.

In a second aspect, the present invention provides pharmaceutical formulations, comprising:

(a) about 0.5% to about 4% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis; and

(b) a peptide of at least 5 contiguous amino acids of Nle3 A(1-7), or salt thereof;

wherein the peptide is present at a concentration of about 0.03% to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

The pharmaceutical formulations are demonstrated herein to be particularly effective for treating diabetic foot ulcers, such as chronic diabetic foot ulcers that are not effectively treated using standard therapies.

In one embodiment, the peptide comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salt thereof. In another embodiment, the peptide consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or salt thereof.

In one embodiment, the peptide, or salt thereof, is present in the formulation at a concentration of about 0.03% to about

6

1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In various further embodiments, the peptide, or salt thereof, is present in the formulation at a concentration of about 0.03% to about 0.75%; about 0.03% to about 0.5%; about 0.03% to about 0.25%; about 0.03% to about 0.1%; about 0.03% to about 0.075%; about 0.03% to about 0.05%; and about 0.03%; all on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

In a further embodiment, the pharmaceutical formulation comprises about 1% to about 3% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. These formulations comprising low percentage HEC (ie: 2%) matrices provided a 10-fold increase in peptide release over a 24 hour period from formulations such as those comprising 10% carboxymethylcellulose (CMC), a result that would be unexpected to those of skill in the art. Furthermore, the data show that the HEC matrices are more biocompatible than HPMC and CMC formulations tested. In a still further embodiment, the pharmaceutical formulation comprises about 2% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis. In another embodiment, the formulation comprises a hydrogel formulation.

In one embodiment, the formulation is topical gel-based formulation selected from the group consisting of hydrogels, creams, ointments, pastes, and lotions. The formulation is administered so as to form a continuous film covering the entire area of the ulcer, including the margins, without running off. In a preferred embodiment, the topical formulation is applied with a thickness of approximately 0.25 to 2 mm; preferably 0.5 to 1.5 mm; preferably about 1 mm in thickness. In another non-limiting embodiment the formulation is applied at approximately 0.075 mL per cm² surface area.

In all aspects and embodiments of the invention, suitable acids which are capable of forming salts with the peptides include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, phosphoric acid and the like; and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, anthranilic acid, cinnamic acid, naphthalene sulfonic acid, sulfanilic acid and the like. Suitable bases capable of forming salts with the peptides include, but are not limited to, inorganic bases such as sodium hydroxide, ammonium hydroxide, potassium hydroxide and the like; and organic bases such as mono-, di- and tri-alkyl and aryl amines (e.g., triethylamine, diisopropyl amine, methyl amine, dimethyl amine and the like) and optionally substituted ethanol-amines (e.g., ethanolamine, diethanolamine and the like).

The pharmaceutical formulations may further comprise (a) a lyoprotectant; (b) a surfactant; (c) a bulking agent; (d) a tonicity adjusting agent; (e) a stabilizer; (f) a preservative and/or (g) a buffer. In some embodiments, the buffer in the pharmaceutical formulations is a Tris buffer, a histidine buffer, a phosphate buffer, a citrate buffer or an acetate buffer. The pharmaceutical formulations may also include a lyoprotectant, e.g. sucrose, sorbitol or trehalose. In certain embodiments, the pharmaceutical formulations includes a preservative e.g. benzalkonium chloride, benzethonium, chlorohexidine, phenol, m-cresol, benzyl alcohol, methylparaben, propylparaben, chlorobutanol, o-cresol, p-cresol, chlorocresol, phenylmercuric nitrate, thimerosal, benzoic acid, and various mixtures thereof. In other embodiments, the pharmaceutical formulations includes a bulking agent, like glycine. In yet other embodiments, the pharmaceutical formulations includes a surfactant e.g., polysorbate-20, polysorbate-40, polysorbate-60, polysorbate-65, polysorbate-80

polysorbate-85, poloxamer-188, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan trilaurate, sorbitan tristearate, sorbitan trioleate, or a combination thereof. The pharmaceutical formulations may also include a tonicity adjusting agent, e.g., a compound that renders the formulation substantially isotonic or isoosmotic with human blood. Exemplary tonicity adjusting agents include sucrose, sorbitol, glycine, methionine, mannitol, dextrose, inositol, sodium chloride, arginine and arginine hydrochloride. In other embodiments, the pharmaceutical formulations additionally includes a stabilizer, e.g., a molecule which, when combined with a protein of interest substantially prevents or reduces chemical and/or physical instability of the protein of interest in lyophilized or liquid form. Exemplary stabilizers include sucrose, sorbitol, glycine, inositol, sodium chloride, methionine, arginine, and arginine hydrochloride.

The peptides or salts thereof can further be derivatized to provide enhanced half-life, for example, by linking to polyethylene glycol. The peptides or salts thereof may comprise L-amino acids, D-amino acids (which are resistant to L-amino acid-specific proteases in vivo), a combination of D- and L-amino acids, and various "designer" amino acids (e.g., β -methyl amino acids, C α -methyl amino acids, and N α -methyl amino acids, etc.) to convey special properties.

The peptide may be the sole active agent in the pharmaceutical composition, or the composition may further comprise one or more other active agents suitable for treating diabetic ulcers.

The formulations may include any other embodiments as disclosed in the example that follows. Such embodiments may be used in any combination in the formulations of the invention, unless the context clearly dictates otherwise.

EXAMPLE

Randomized, Parallel-Group, Double-Blind,
Placebo-Controlled Phase 2 Clinical Trial to
Evaluate the Safety and Effectiveness of
NorLeu³-A(1-7) in Treating Subjects with Diabetic
Ulcers

The study was designed as a randomized, parallel-group, double-blind, placebo-controlled, multi-center trial. After 14-days of best-of-care to evaluate ulcer healing and ensure the wounds were chronic, four-weeks of active treatment were then followed by eight weeks of observation and assessment. The study compared the effects of two concentrations of NorLeu³-A(1-7) and placebo, measuring both clinical efficacy and safety. Sustained tissue integrity was evaluated for all subjects during a follow-up period lasting 12 weeks after complete wound closure.

Subjects were randomized in a 1:1:1 ratio to one of the three treatment groups:

Group 1: Placebo Vehicle Control without NorLeu³-A(1-7) (also referred to as "DSC127") (2% Hydroxyethyl Cellulose (HEC) with 0.1% methyl paraben, 0.02% propyl paraben)

Group 2: 0.03% NorLeu³-A(1-7) in Vehicle

Group 3: 0.01% NorLeu³-A(1-7) in Vehicle

The four-week treatment period required daily application of the treatment to the wound site. The first application each week was at the clinic and for the remainder of the week the patient self-administered the treatment.

If wound healing occurred during the treatment or assessment periods a final assessment visit was conducted and the integrity was assessed 4 and 12 weeks later (usually weeks 16 and 24 of the study).

Inclusion Criteria

The following patients were considered eligible for participation in the study:

- 1) Male or female ambulatory subjects who were at least 18 years of age at screening
- 2) At start of Screening Period and upon enrollment into the study, had at least one chronic non-healing Wagner Grade 1 or Grade 2 (ulcers of partial or full thickness and not involving bone, tendon or capsule (probing to tendon or capsule), and that have no sign of infection or myelitis) plantar neuropathic diabetic ulcer between 1.0-6.0 cm² on the midfoot or forefoot, including the toes but excluding the heel. Non-healing is defined as present for a minimum of one month but not longer than ten months with less than 30% reduction in size in response to treatment (non-study treatment, but including off-loading) during the Screening Period. If more than one ulcer is present that meets the inclusion criteria, the larger was studied and treated according to the protocol. Non-study ulcers were treated according to institutional best practice, using per protocol offloading.
- 3) Have an Ankle Brachial Index (ABI) greater than 0.7 for neuroischemic or greater than 0.8 for neuropathic DFU.
- 4) Have a Tissue Oxygen Pressure (TcPO₂) greater than 40 mm Hg or great toe systolic pressure greater than 50 mmHg to ensure healing potential.
- 5) Have Type I or Type II diabetes under metabolic control as confirmed by a glycosylated hemoglobin (HbA_{1c}) of less than or equal to 12%, and a serum creatinine level of no greater than 3 mg/dL obtained within 3 months of study enrollment.
- 6) Assess the baseline level of neuropathy of the foot using Semmes-Weinstein filaments. Patients were considered to have site specific neuropathy sufficient for loss of protective sensation (LOPS) if they were unable to feel a #5.07 monofilament applied to at least 5 of the following 7 sites (28) on the study foot:
plantar to toes and metatarsals 1, 3 and 5 (3 sites)
plantar to midfoot medial and lateral (2 sites)
plantar heel (1 site)
dorsal distal first interspace (1 site)
- 7) Female subjects of child-bearing potential must have negative pregnancy test at the time of initiation of study therapy.
- 8) Female subjects of child-bearing potential must have been willing to use a medically acceptable method of birth control, such as Essure®, hormonal contraception (oral pills, implantable device or skin patch), intrauterine device, tubal ligation or double barrier, during the treatment and assessment period of study participation.
- 9) Ability and willingness to understand and comply with study procedures and to give written informed consent prior to enrollment in the study or initiation of study procedures.

Exclusion Criteria

If a subject met any of the following criteria, he or she was excluded from the study:

- 1) Has a known hypersensitivity to any of the study medication components.
- 2) Exposure to any investigational agent within 30 days of entry into study.
- 3) Females who are pregnant or nursing.

37

- 4) Females unwilling to use a medically acceptable method of birth control, such as Essure®, hormonal contraception (oral pills, implantable device or skin patch), intrauterine device, tubal ligation or double barrier, during the treatment and assessment period of study participation.
- 5) Active malignant disease of any kind A subject, who has had a malignant disease in the past, was treated and is currently disease-free, may be considered for study entry.
- 6) Chronic renal insufficiency (serum creatinine during screening is greater than 3.0 g/dL obtained within 3 months of study enrollment).
- 7) Chronic liver dysfunction evidenced by transaminase levels greater than twice normal.
- 8) Receiving hemodialysis or chronic ambulatory peritoneal dialysis (CAPD) therapy.
- 9) Resting blood pressure (at the time of the initial visit of the Screening Period) which exceeds 160 systolic and/or 90 diastolic mmHg on 3 consecutive readings at least 15 minutes apart.
- 10) Prior radiation therapy of the foot with the ulcer under study.
- 11) Current use of corticosteroids (within past 8 weeks), immunosuppressants (within past 8 weeks).
- 12) Known to be HIV positive.
- 13) Subjects whose ulcer was primarily ischemic in etiology as diagnosed by an ABI of <0.7 or great toe systolic pressure <40 mmHg or TcPO₂<40 mmHg in the supine position and <40 mmHg while sitting, measured on the forefoot with electrode set at 44 C.
- 14) Sickle-cell anemia, Raynaud's or other peripheral vascular disease.
- 15) Current history of drug abuse.
- 16) Subjects receiving a biologic agent to include growth factors and skin equivalents (Regranex™, Apligraf™, or Dermagraft™) in the past 30 days.
- 17) Subjects with uncontrolled diabetes defined as a glycosylated hemoglobin (HbA_{1c})>12%, or a serum creatinine level of greater than 3 g/dL obtained within 3 months of study enrollment determined on two separate occasions at least 3 weeks apart.
- 18) Subject with an ulcer which is determined to be clinically infected and requires topical antimicrobials or agents known to affect wound healing or has been taking systemic antibiotics for more than 7 days for any reason.
- 19) Subject with a Wagner Grade 3 or higher DFU, deep abscess or infection of the joint or tendon, or gangrene or osteomyelitis.
- 20) An EKG with a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of QTc interval >450 milliseconds (ms))

A total of 80 subjects were enrolled in the study; 27 were randomized to the 0.03% dose of NorLeu³-A(1-7), 25 were randomized to placebo and 28 were randomized to the 0.01% dose. All subjects also received best standard of care, which included debridement, wound cleansing, application of an occlusive dressing and standardized proper off-loading.

Results

Recent results from a Phase 2 clinical trial with NorLeu³-A(1-7) in patients with diabetic foot ulcers showed that the proportion of study ulcers healed by 12 weeks as defined by 100% epithelialized with no drainage, as well as all secondary endpoints. The double-blind, placebo-controlled, multi-center clinical trial randomized 80 subjects to receive one of two doses of NorLeu³-A(1-7) (0.03% and 0.01%) or vehicle placebo (2% hydroxyethyl cellulose in phosphate buffer with 0.1% methyl paraben and 0.02% propyl paraben) control, in

addition to best standard of care (which included debridement). The drug was well-tolerated and there were no significant adverse events associated with NorLeu³-A(1-7) treatment.

In the Intent-to-Treat (ITT) population (all subjects receiving any study medication and from whom any post-baseline data are available): Results show that 54% of the diabetic wounds treated with 0.03% (high dose) of NorLeu³-A(1-7) achieved 100% closure in 12 weeks or less, compared with 33% of patients receiving placebo control, and 30% of patients receiving the 0.01% dose (low dose) of NorLeu³-A(1-7). Based on odds ratio analysis, patients treated with NorLeu³-A(1-7) 0.03% were 2.3 times more likely to have their wounds heal completely as compared to patients treated with placebo/standard of care.

In the Per Protocol (PP) population (all patients that did not have a major protocol violation affecting efficacy): Results show that 65% of the diabetic wounds treated with 0.03% dose of NorLeu³-A(1-7) achieved 100% closure in 12 weeks or less, compared with 38% of patients receiving placebo control, and 28% of patients receiving the 0.01% dose of NorLeu³-A(1-7). See FIGS. 1-3. Based on odds ratio analysis, patients treated with NorLeu³-A(1-7) 0.03% were 3.0 times more likely to have their wounds heal completely as compared to patients treated with placebo/standard of care.

The high dose of NorLeu³-A(1-7) well exceeded the trial's primary endpoint measurement target of an improvement of 15 percentage points in complete healing of wounds within the 12-week duration of the study for both the ITT (21% increase) and PP (27% increase) populations compared with placebo.

The trial was not powered for statistical significance, however there was a statistically significant (p=0.049) 50% improvement in the rate of healing in the PP high-dose population through 12 weeks of treatment compared with the control arm, as measured by depth of ulcer using covariate analysis.

The wound healing rates for patients on NorLeu³-A(1-7) were remarkable with the ITT analysis showing a 21% increase and the PP analysis showing a 27% increase over the placebo arm.

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We claim:

1. A pharmaceutical formulation, comprising:
 - (a) 0.5% to 4% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis; and
 - (b) a peptide of at least 5 contiguous amino acids of Nle3 A(1-7), or a salt thereof;
 wherein the peptide, or salt thereof is present at a concentration of about 0.03% to about 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.
2. The pharmaceutical formulation of claim 1, wherein the peptide, or salt thereof comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1) or a salt thereof.
3. The pharmaceutical formulation of claim 1, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1) or a salt thereof.
4. The pharmaceutical formulation of claim 1, comprising 1% to 3% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.
5. The pharmaceutical formulation of claim 1 comprising 2% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.
6. The pharmaceutical formulation of claim 1, wherein the formulation comprises a hydrogel formulation.
7. The pharmaceutical formulation of claim 1, wherein the peptide, or salt thereof, is present at a concentration of about 0.03% to about 0.5% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.
8. The pharmaceutical formulation of claim 1, wherein the formulation is selected from the group consisting of a cream, an ointment, a paste, and a lotion.
9. The pharmaceutical formulation of claim 1, wherein the formulation further comprises one or more of (a) a lyoprotectant; (b) a surfactant; (c) a bulking agent; (d) a tonicity adjusting agent; (e) a stabilizer; (f) a preservative and (g) a buffer.
10. The pharmaceutical formulation of claim 1, further comprising one or more other active agents suitable for treating diabetic ulcers.
11. The pharmaceutical formulation of claim 4, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
12. The pharmaceutical formulation of claim 5, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
13. The pharmaceutical formulation of claim 6, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
14. The pharmaceutical formulation of claim 7, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
15. The pharmaceutical formulation of claim 8, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
16. The pharmaceutical formulation of claim 9, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
17. The pharmaceutical formulation of claim 10, wherein the peptide, or salt thereof consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1), or a salt thereof.
18. A method for treating diabetic foot ulcers, comprising administering to a human patient suffering from a diabetic foot ulcer an amount of a pharmaceutical formulation according to claim 1 effective to treat the diabetic foot ulcer.
19. The method of claim 18, wherein the peptide, or salt thereof, comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1).
20. The method of claim 18, wherein the peptide, or salt thereof, consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1).

40

15

21. The method of claim 18, wherein the diabetic foot ulcer is one caused, at least in part, by neuropathy and resulting pressure.

22. The method of claim 18, wherein the diabetic foot ulcer comprises one or more calluses.

23. The method of claim 18, wherein the diabetic foot ulcer is a chronic ulcer.

24. The method of claim 23, wherein the chronic foot ulcer has not responded to any other treatment.

25. The method of claim 18, wherein the peptide, or salt thereof, is administered topically.

26. The method of claim 25, wherein the peptide, or salt thereof, is administered as a topical formulation forming a continuous film covering the entire area of the diabetic ulcer.

27. The method of claim 25, wherein the peptide, or salt thereof, is administered in a hydrogel formulation.

* * * * *

16



(11) **EP 2 536 422 B1**

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(54) **METHODS FOR TREATING DIABETIC FOOT ULCERS**

VERFAHREN ZUR BEHANDLUNG VON DIABETISCHEN FUSSGESCHWÜREN

PROCÉDÉS DE TRAITEMENT D'ULCÈRES DU PIED DIABÉTIQUE

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Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 536 422 B1

the peptide comprises Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1).

12. The pharmaceutical formulation of claim 10, wherein the peptide consists of Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1).
13. The pharmaceutical formulation of any one of claims 10-12, comprising 1% to 3% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.
14. The pharmaceutical formulation of any one of claims 10-12, comprising 2% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.
15. The pharmaceutical formulation of any one of claims 10-14, wherein the formulation comprises a hydrogel formulation.

Patentansprüche

1. Peptid aus mindestens 5 benachbarten Aminosäuren von Nle3 A(1-7) zur Verwendung in der Behandlung von diabetischen Fußgeschwüren bei einem humanen Patienten, wobei das Peptid aus mindestens 5 benachbarten Aminosäuren von Nle3 A(1-7) in einer Menge verabreicht wird, die wirksam ist, um das diabetische Fußgeschwür zu behandeln, und wobei das Peptid topisch in einer Gelformulierung verabreicht wird, die 0,5% bis 4% Hydroxyethylcellulose (HEC) auf einer Gewichts- (mg) / Volumen- (ml) Basis oder auf einer Gewichts- / Gewichts- (mg) Basis umfasst.
2. Peptid zur Verwendung nach Anspruch 1, wobei das Peptid Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NR. 1) umfasst.
3. Peptid zur Verwendung nach Anspruch 1, wobei das Peptid aus Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NR. 1) besteht.
4. Peptid zur Verwendung nach einem der Ansprüche 1 bis 3, wobei das diabetische Fußgeschwür eines ist, das zumindest teilweise, durch Neuropathie und resultierendem Druck verursacht ist.
5. Peptid zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das diabetische Fußgeschwür ein oder mehrere Kallusse umfasst.
6. Peptid zur Verwendung nach einem der Ansprüche 1 bis 5, wobei das diabetische Fußgeschwür ein chronisches Geschwür ist, und wobei das chronische Fußgeschwür vorzugsweise nicht auf eine andere Behandlung angesprochen hat.

7. Peptid zur Verwendung nach einem der Ansprüche 1 bis 6, wobei das Peptid als eine topische Formulierung verabreicht wird, die einen zusammenhängenden Film bildet, der das gesamte Gebiet des diabetischen Geschwürs abdeckt.

8. Peptid zur Verwendung nach Anspruch 7, wobei das Peptid in einer Hydrogelformulierung verabreicht wird.

9. Peptid zur Verwendung nach einem der Ansprüche 1 bis 8, wobei das Peptid in einer Konzentration von 0,03% bis 1% auf einer Gewichts- (mg) / Volumen- (ml) Basis oder auf einer Gewichts- / Gewichts- (mg) Basis verabreicht wird.

10. Pharmazeutische Formulierung, umfassend:

a. 0,5% bis 4% HEC auf einer Gewichts- (mg) / Volumen- (ml) Basis oder auf einer Gewichts- / Gewichts- (mg) Basis; und

b. ein Peptid aus mindestens 5 benachbarten Aminosäuren von Nle3 A(1-7); wobei das Peptid in einer Konzentration von 0,03% bis 1% auf einer Gewichts- (mg) / Volumen- (ml) Basis oder auf einer Gewichts- / Gewichts- (mg) Basis vorliegt.

11. Pharmazeutische Formulierung nach Anspruch 10, wobei das Peptid Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NR. 1) umfasst.

12. Pharmazeutische Formulierung nach Anspruch 10, wobei das Peptid aus Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NR. 1) besteht.

13. Pharmazeutische Formulierung nach einem der Ansprüche 10 bis 12, welche 1% bis 3% HEC auf einer Gewichts- (mg) / Volumen- (ml) Basis oder auf einer Gewichts- / Gewichts- (mg) Basis umfasst.

14. Pharmazeutische Formulierung nach einem der Ansprüche 10 bis 12, welche 2% HEC auf einer Gewichts- (mg) / Volumen- (ml) Basis oder auf einer Gewichts- / Gewichts- (mg) Basis umfasst.

15. Pharmazeutische Formulierung nach einem der Ansprüche 10 bis 14, wobei die Formulierung eine Hydrogelformulierung umfasst.

Revendications

1. Peptide d'au moins 5 acides aminés contigus de Nle3 A(1-7) pour son utilisation pour traiter les ulcères du pied diabétique chez un patient humain, dans lequel le peptide d'au moins 5 acides aminés contigus de Nle3 A(1-7) est administré en une quantité

43

- efficace pour traiter l'ulcère du pied diabétique et dans lequel le peptide est administré par voie topique dans une formulation de gel qui comprend 0,5 % à 4 % d'hydroxyéthyl-cellulose (HEC) sur une base poids (mg)/volume (ml) ou sur une base poids/poids (mg).
2. Peptide pour son utilisation selon la revendication 1, dans lequel le peptide comprend Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO : 1).
 3. Peptide pour son utilisation selon la revendication 1, dans lequel le peptide consiste en Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO : 1).
 4. Peptide pour son utilisation selon l'une quelconque des revendications 1 à 3, dans lequel l'ulcère du pied diabétique est causé, au moins en partie, par une neuropathie et la pression en résultant.
 5. Peptide pour son utilisation selon l'une quelconque des revendications 1 à 4, dans lequel l'ulcère du pied diabétique comprend une ou plusieurs callosités.
 6. Peptide pour son utilisation selon l'une quelconque des revendications 1 à 5, dans lequel l'ulcère du pied diabétique est un ulcère chronique et dans lequel l'ulcère du pied chronique n'a de préférence répondu à aucun autre traitement.
 7. Peptide pour son utilisation selon l'une quelconque des revendications 1 à 6, dans lequel le peptide est administré sous la forme d'une formulation topique formant un film continu couvrant la surface entière de l'ulcère diabétique.
 8. Peptide pour son utilisation selon la revendication 7, dans lequel le peptide est administré dans une formulation d'hydrogel.
 9. Peptide pour son utilisation selon l'une quelconque des revendications 1 à 8, dans lequel le peptide est administré en une concentration de 0,03 % à 1 % sur une base poids (mg)/volume (ml) ou sur une base poids/poids (mg).
 10. Formulation pharmaceutique, comprenant :
 - (a) 0,5 % à 4 % d'HEC sur une base poids (mg)/volume (ml) ou sur une base poids/poids (mg) ; et
 - (b) un peptide d'au moins 5 acides aminés contigus de Nle3 A(1-7);
 dans laquelle le peptide est présent en une concentration de 0,03 % à 1 % sur une base poids (mg)/volume (ml) ou sur une base poids/poids (mg).
 11. Formulation pharmaceutique selon la revendication 10, dans laquelle le peptide comprend Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO : 1).
 12. Formulation pharmaceutique selon la revendication 10, dans laquelle le peptide consiste en Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO : 1).
 13. Formulation pharmaceutique selon l'une quelconque des revendications 10 à 12, comprenant 1 % à 3 % d'HEC sur une base poids (mg)/volume (ml) ou sur une base poids/poids (mg).
 14. Formulation pharmaceutique selon l'une quelconque des revendications 10 à 12, comprenant 2 % d'HEC sur une base poids (mg)/volume (ml) ou sur une base poids/poids (mg).
 15. Formulation pharmaceutique selon l'une quelconque des revendications 10 à 14, dans laquelle la formulation comprend une formulation d'hydrogel.

	PRE-FACTURA TRÁMITE INTERNACIONAL DEPARTAMENTO DE PATENTES		CÓDIGO DOCUMENTO	I-PEPN-3.9-1 PATENTES
			VERSIÓN	3
			FECHA VERSIÓN	15.07.2013
			PÁGINA	1 de 1
ELABORÓ CHR/DIRECTOR DE PATENTES		REVISÓ REPRESENTANTE DE CALIDAD	APROBÓ DIRECTOR GENERAL	

PREFACTURA INTERNACIONAL					
SOLICITANTE: INSTITUCION UNIVERSITARIA COLEGIO MAYOR DE ANTIOQUIA Y JUAN CAMILO					
FACTURA A NOMBRE DE: INSTITUCION UNIVERSITARIA COLEGIO MAYOR DE ANTIOQUIA					
S/Ref: PCT/IB2013051381					
N/Ref: P-4712					
PERSONA DE CONTACTO: ANGELA MARIA GAVIRIA					
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DIRECCION DE ENVIO: CORREO FISICO					
NIT:					
DESCRIPCION Y VALORES A FACTURAR CODIGO 001-0004-000004 y 001-0004-000020					
FACTURACION EN		PESOS	x	DÓLAR	EURO
CONCEPTO : Presentación Poderes ante el Registro. Solicitud de Patente en Guatemala Traducción Apostillas de los Poderes					
HONORARIOS		YEN		DÓLAR	EURO
				95.4	
GASTOS REEMBOLSABLES					
Gastos legalizaciones - apostillas (COP)					
Gastos: copias, courier, correos (COP)					
Honorarios y gastos corresponsal extranjero*		YEN		DÓLAR	EURO
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*NOTA: Este valor debe ser exacto al valor de la factura					
COTIZACION		CONTRATO			
VALOR DE LA COTIZACION					
ELABORA PROYECTO			APROBADO POR		
FRANCIA GARCIA Paralegal			Jefe Depto. Internacional		

45

	PRE-FACTURA TRÁMITE INTERNACIONAL DEPARTAMENTO DE PATENTES		CÓDIGO DOCUMENTO	I-PEPN-3.9-1 PATENTES
			VERSIÓN	3
			FECHA VERSIÓN	15.07.2013
			PÁGINA	1 de 1
ELABORÓ CHR/DIRECTOR DE PATENTES	REVISÓ REPRESENTANTE DE CALIDAD	APROBÓ DIRECTOR GENERAL		

PREFACTURA INTERNACIONAL				
SOLICITANTE: INSTITUCION UNIVERSITARIA COLEGIO MAYOR DE ANTIOQUIA Y JUAN CAMILO				
FACTURA A NOMBRE DE: INSTITUCION UNIVERSITARIA COLEGIO MAYOR DE ANTIOQUIA				
S/Ref: PCT/IB2013/051381				
N/Ref: P-4713				
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DIRECCION DE ENVIO: CORREO FISICO				
NIT:				
DESCRIPCION Y VALORES A FACTURAR CODIGO 001-0004-000004				
FACTURACION EN	PESOS	x	DÓLAR	EURO
CONCEPTO : Presentación Tardía Cesión Solicitud de Patente en Perú				
HONORARIOS	YEN		DÓLAR	EURO
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COTIZACION		CONTRATO		
VALOR DE LA COTIZACION				
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46



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January 22, 2014
Via e-mail only

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Re: Y/R: 11-1000-PCT-JP O/R: PF 10228
Japanese Patent Application No. 2013-502927
'METHODS FOR TREATING DIABETIC FOOT ULCERS'
- UNIVERSITY OF SOUTHERN CALIFORNIA -

Dear Dr. Harper:

We are pleased to inform you that the examiner has decided to grant a patent for this application. We are enclosing a copy of a Certified Copy of the Notice of Allowance. In order to have a patent registered and issued from the application, the registration fee (i.e., the 1st to 3rd year annuities) must be paid by February 20, 2014. The official fee is 14,100 yen, and the attorney's fee is 17,000 yen. Further, we charge 9,000 yen and miscellaneous expenses for forwarding a Certificate of Patent. If possible, please provide us with your instructions by February 10, 2014 as to whether we should proceed with paying the registration fee.

After payment of the registration fee, a patent will be issued and later published.

We look forward to receiving your instructions.

Very truly yours,

ONDA TECHNO
Intl. Patent Attys.

Yuko Toyoshima
Yuko Toyoshima (Ms.)

YT/co
Encls.

47

O/R: PF 10228

Forwarding Number: 028426
Forwarding Date: January 21, 2014

CERTIFIED COPY OF THE NOTICE OF ALLOWANCE

Patent Application No. 2013-502927
Date: January 17, 2014
The Examiner of the Patent Office: Koichiro TANAKA
Reg. No. 9636 4U00
Title of the Invention: METHODS FOR TREATING DIABETIC FOOT
ULCERS
Number of Claims: 12
Applicant for Patent Application:
UNIVERSITY OF SOUTHERN CALIFORNIA
Agent: Makoto ONDA (et al.)

[Pretrial Examination]

The Decision of Rejection is to be withdrawn.

As no reason of rejection is found, it is admitted that this application is to be patented.

This is to certify that this certified copy is not different from the record in our file.

Certified Date: January 20, 2014

Secretary of Ministry of
Economy, Trade and Industry

68

特許査定

特許出願の番号	特願2013-502927
起案日	平成26年 1月17日
特許庁審査官	田中 耕一郎 9636 4U00
発明の名称	糖尿病性足部潰瘍を処置するための方法
請求項の数	12
特許出願人	ユニバーシティー オブ サザン カリフォル ニア
代理人	恩田 誠 (外 2名)

〔前置審査〕

原査定を取消す。

この出願については、拒絶の理由を発見しないから、特許査定をします。



上記はファイルに記録されている事項と相違ないことを認証する。

認証日 平成26年 1月20日 経済産業事務官 清野 貴明

注意: この書面を受け取った日から30日以内に特許料の納付が必要です。

49

The claim set filed for appeal

1. (currently amended) A pharmaceutical formulation for treating diabetic foot ulcers, comprising: (a) 0.5% to 4% hydroxyethyl cellulose (HEC) on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis; and (b) a peptide consisting of ~~comprising~~ Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO:1) Nle3 A(1-7); wherein the peptide is present at a concentration of 0.03% to 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

2. (Canceled)

2[[3]]. The pharmaceutical formulation of claim 1, comprising 1% to 3% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

3[[4]]. The pharmaceutical formulation of claim 1, comprising 2% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

4[[5]]. The pharmaceutical formulation of claim 1, wherein the formulation comprises a hydrogel formulation.

6-8. (Canceled)

5[[9]]. (currently amended) A composition for treating diabetic foot ulcers, comprising an amount of a peptide consisting of ~~comprising~~ Asp-Arg-Nle-Tyr-Ile-His-Pro (SEQ ID NO: 1) effective to treat the diabetic foot ulcer, characterized in that the composition is administered topically in a gel formulation that comprises 0.5% to 4% HEC on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

December 19, 2013

Dr. David Harper

Y/R: 11-1000-PCT-JP O/R: PF 10228

~~10~~. (Canceled)

6[[11]]. The composition of claim 5[[9]], wherein the diabetic foot ulcer is one caused, at least in part, by neuropathy and resulting pressure.

7[[12]]. The composition of claim 5[[9]], wherein the diabetic foot ulcer comprises one or more calluses.

8[[13]]. The composition of claim 5[[9]], wherein the diabetic foot ulcer is a chronic ulcer.

9[[14]]. The composition of claim 8[[13]], wherein the chronic foot ulcer has not responded to any other treatment.

10[[15]]. The composition of claim 5[[9]], characterized in that the composition is administered as a topical formulation forming a continuous film covering the entire area of the diabetic ulcer.

11[[16]]. The composition of claim 5[[9]], characterized in that the composition is administered in a hydrogel formulation.

12[[17]]. The composition of claim 5[[9]], characterized in that the composition is administered at a concentration of 0.03% to 1% on a weight (mg)/volume (ml) basis, or on a weight/weight (mg) basis.

~~18-24~~. (Canceled)