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DIRECCIÓN DE NUEVAS CREACIONES
Procedimiento acelerado de exámenes de patente (PPH)

1	NÚMERO DE SOLICITUD ANTE LA SIC NC2022/0000660		
2	GLOBAL - PPH ☐ PAÍS	3	PCT – PPH ☐ PAÍS
4	PROSUR ☐ PAÍS	5	Alianza del Pacifico (AdP) ☐ PAÍS
6	OFICINA DE PRIMERA PRESENTACIÓN (OPP) ☒	7	OFICINA DE EXAMEN ANTERIOR (OEA) ☐
8	NÚMERO DE SOLICITUD O PUBLICACIÓN DE LA SOLICITUD (OPP) ☒ NÚMERO DE SOLICITUD EN OFICINA DE EXAMEN ANTERIOR (OEA): ☐ NÚMERO DE SOLICITUD PCT: ☐		Solicitud US16/996,030; Publicación US20210206832A1 Patente No. US11104715B2
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
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DIRECCIÓN	Carrera 11 No. 86-53 Piso 3	No. TELÉFONO	6181088
CIUDAD	Bogotá	CORREO ELECTRÓNICO	notificaciones@clark emodet.com.co
PAÍS	COLOMBIA	No. RADICACIÓN O PROTOCOLO DE PODER GENERAL	
10	CONDICIONES PARA ACCEDER A ESTE PROCESO:		
10.1.	DATOS DE PRIORIDAD ☒ SI ☐ NO		
(33) PAÍS DE ORIGEN		CÓDIGO PAÍS	(31) NÚMERO
1. UNITED STATES OF AMERICA		US	63/065,012
2. UNITED STATES OF AMERICA		US	62/944,635
(32) FECHA (AAAA/MM/DD)			
2020/08/13			
2019/12/06			
10.2.	DATOS SOLICITUD INTERNACIONAL PCT ☒ SI ☐ NO		
Solicitud Internacional No.	PCT/US2020/046823	Fecha	2020/08/18
Publicación Internacional No.	WO/2021/112924	Fecha	2021/06/10
*El solicitante presenta una copia de la(s) reivindicación(es) patentable(s) u otorgable(s) de la solicitud de la Oficina de Primera Presentación que profirió el examen de patentabilidad, junto con una traducción al castellano. ☒ SI ☐ NO			
*El solicitante presenta los resultados de búsqueda de la Oficina de Examen Anterior, junto con una traducción al castellano ☒ SI ☐ NO			
REQUISITOS PARA EL RECONOCIMIENTO DE LOS RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS A SOLICITUDES EXTRANJERAS			
Para que la Superintendencia de Industria y Comercio pueda reconocer los resultados de exámenes de patentabilidad producidos por otras Oficinas de Propiedad Industrial se debe cumplir con las siguientes condiciones:			
(a) Al momento de solicitar el examen de patentabilidad, si el solicitante pide que se reconozcan exámenes de patentabilidad de otras oficinas extranjeras, deberá aportar junto con el pago de la tasa correspondiente, los siguientes anexos:			
(i) Copia de las resoluciones, fallos o decisiones que han sido relevantes para la determinación de la patentabilidad de la(s) solicitud(es) en la Oficina que haya proferido el examen de patentabilidad que contienen reivindicaciones patentables u otorgables que son la base de la petición, y si es del caso, su traducción al castellano. ☒ SI ☐ NO			
(ii) Copia de todas las reivindicaciones determinadas como patentables u otorgables en la Oficina que profirió el examen de patentabilidad y, si es del caso, su traducción al castellano. ☒ SI ☐ NO			
(iii) Copia de los antecedentes, información o documentos citados por el examinador de la Oficina de Primera Presentación del examen de patentabilidad, en las resoluciones, fallos o decisiones correspondientes, incluyendo la literatura no patente. Los documentos de patente deberán presentarse siempre y cuando no estén disponibles para la Superintendencia de Industria y Comercio mediante el simple acceso a bases de datos gratuitas. ☒ SI ☐ NO			
(iv) Una tabla de correspondencias de las reivindicaciones que han sido determinadas como patentables u otorgables en la solicitud de la Oficina que haya proferido el examen de patentabilidad. ☒ SI ☐ NO			
11	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL <i>Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)</i>		
 CAROLINA DAZA MONTALVO			

10 (iv)	TABLA DE CORRESPONDENCIA DE REIVINDICACIONES				
Reivindicaciones en la solicitud en Colombia (NOTA. LAS REIVINDICACIONES ACÁ INDICADAS CORRESPONDEN A AQUELLAS MODIFICADAS POR MODIFICACIÓN VOLUNTARIA DEL 30 DE JUNIO DE 2022)		Reivindicaciones otorgables por la Oficina Estadounidense de patentes para la solicitud US16/996,030	Explicación sobre la suficiente correspondencia ó Comentarios que explican la correspondencia		
1.	Un método para producir aflibercept recolectado a partir una célula hospedera cultivada en un medio químicamente definido (CDM), que comprende: (a) proporcionar una célula hospedera diseñada por ingeniería genética para expresar aflibercept; (b) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales dicha célula expresa aflibercept, en donde la concentración acumulativa de níquel en dicho CDM es menor o igual a 0,4 µM, o alrededor de 0,4 µM, y uno o más de los siguientes: i. la concentración acumulativa de hierro en dicho CDM es mejor que, o igual a, 55,0 µM; ii. la concentración acumulativa de cobre en dicho CDM es menor que, o igual a 0,8 µM; iii. la concentración acumulativa de zinc en dicho CDM es menor que, o igual a, 56,0 µM; iv. la concentración acumulativa de cisteína en dicho CDM es menor que, o igual a, 10,0 µM, y v. dicho CDM contiene antioxidantes, en donde la concentración acumulativa de un antioxidante está entre 0,001 mM y 10,0 mM aproximadamente para cualquier antioxidante individual; y (c) recolectar el aflibercept producido por la célula hospedera..	18.	Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende: (a) proporcionar una célula hospedera diseñada por ingeniería genética para expresar aflibercept; (b) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 µM o aproximadamente 0,4 µM y uno o más de los siguientes; i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 µM; ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 µM; iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 µM; iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM; y v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM a aproximadamente 10,0 mM para cualquier antioxidante único; y (c) recolectar el aflibercept producido por tal célula hospedera.	Corresponde a la reivindicación 1 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.	
2.	El método de conformidad con la reivindicación 1, en donde dicha recolección tiene un color no más amarillo-marrón que el color europeo estándar BY2, en donde la concentración de aflibercept es 5,0 g/L.	19.	El método de conformidad con la reivindicación 10, caracterizado porque tal recolección tiene un color no más amarillo-marrón que el Estándar Europeo de Color BY2, en donde la concentración de aflibercept es 5,0 g/l.		Corresponde a la reivindicación 2 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.
3.	El método de conformidad con la reivindicación 2, en donde los antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatión, colina, hidrocortisona, vitamina C, Vitamina E o una combinación de los mismos.	20.	El método de conformidad con la reivindicación 11, caracterizado porque tales antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatión, colina, hidrocortisona, Vitamina C, Vitamina E o combinaciones de los mismos.		Corresponde a la reivindicación 3 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.
4.	El método de conformidad con la reivindicación 2, en donde la concentración acumulativa de un antioxidante en tal CDM es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para	21.	El método de conformidad con la reivindicación 11, caracterizado porque tal concentración acumulativa de un antioxidante en tal CDM es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para cualquier		Corresponde a la reivindicación 4 de la solicitud colombiana, en

<i>cualquier anti-oxidante único, y la concentración acumulativa de todos los antioxidantes es menor o igual a 30,0 mM.</i>	<i>antioxidante único y la concentración acumulativa de todos los antioxidantes es aproximadamente 30,0 mM o menos de 30,0 mM.</i>	<i>donde se ajustó la numeración y la dependencia.</i>
5. <i>El método de conformidad con la reivindicación 1, en donde porque el titular de aflibercept, la concentración de células viables, la viabilidad, el amoníaco o la osmolalidad permanecen sustancialmente inalterados.</i>	30. <i>El método de conformidad con la reivindicación 10, caracterizado porque el titular de aflibercept, concentración celular viable, viabilidad, amoníaco u osmolalidad está sustancialmente sin cambio.</i>	<i>Corresponde a la reivindicación 5 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.</i>
6. <i>El método de conformidad con la reivindicación 1, caracterizado porque tal célula hospedera se selecciona a partir del grupo que consiste de CHO, NS0, Sp2/0, células renales embrionarias y BHK.</i>	9. <i>El método de conformidad con la reivindicación 18, caracterizado porque tal célula hospedera se selecciona a partir del grupo que consiste de CHO, NS0, Sp2/0, células renales embrionarias y BHK.</i>	<i>Corresponde a la reivindicación 6 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.</i>
7. <i>El método de conformidad con la reivindicación 1, caracterizado porque tal recolección comprende una o más variantes de aflibercept, en donde tales variantes tienen al menos un residuo de aminoácido oxidado.</i>	10. <i>El método de conformidad con la reivindicación 18, caracterizado porque tal recolección comprende una o más variantes de aflibercept, en donde tales variantes tienen al menos un residuo de aminoácido oxidado.</i>	<i>Corresponde a la reivindicación 7 de la solicitud colombiana en donde se ajustó la numeración y la dependencia.</i>
8. <i>El método de conformidad con la reivindicación 7, caracterizado porque tal residuo de aminoácido oxidado se selecciona a partir del grupo que consiste de metionina, triptófano, histidina, fenilalanina, tirosina y una combinación de las mismas.</i>	11. <i>El método de conformidad con la reivindicación 10, caracterizado porque tal residuo de aminoácido oxidado se selecciona a partir del grupo que consiste de metionina, triptófano, histidina, fenilalanina, tirosina y una combinación de las mismas.</i>	<i>Corresponde a la reivindicación 8 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.</i>
9. <i>El método de conformidad con la reivindicación 8, caracterizado porque tal residuo de aminoácido oxidado es histidina.</i>	12. <i>El método de conformidad con la reivindicación 11, caracterizado porque tal residuo de aminoácido oxidado es histidina.</i>	<i>Corresponde a la reivindicación 9 de la solicitud colombiana en donde se ajustó la numeración y la dependencia.</i>
10. <i>El método de conformidad con la reivindicación 8, caracterizado porque tal residuo de aminoácido oxidado es triptófano.</i>	13. <i>El método de conformidad con la reivindicación 11, caracterizado porque tal residuo de aminoácido oxidado es triptófano.</i>	<i>Corresponde a la reivindicación 10 de la solicitud colombiana en donde se ajustó la numeración y la dependencia.</i>
11. <i>El método de conformidad con la reivindicación 7, caracterizado porque tal variante de aflibercept comprende un polipéptido que tiene una secuencia de aminoácido seleccionada a partir del grupo que consiste de: SEQ ID NO.: 17, SEQ ID NO.: 18, SEQ ID NO.: 19, SEQ ID NO.: 20, SEQ ID NO.: 21, SEQ ID NO.: 22, SEQ ID NO.: 23, SEQ ID NO.: 62, SEQ ID NO.: 63, SEQ ID NO.: 64, SEQ ID NO.: 65, SEQ ID NO.: 66, SEQ ID NO.: 67, SEQ ID NO.: 68, SEQ ID NO.: 69, SEQ ID NO.: 70, SEQ ID NO.: 71 y combinaciones de las mismas.</i>	14. <i>El método de conformidad con la reivindicación 10, caracterizado porque tal variante de aflibercept comprende un polipéptido que tiene una secuencia de aminoácido seleccionada a partir del grupo que consiste de: SEQ ID NO.: 17, SEQ ID NO.: 18, SEQ ID NO.: 19, SEQ ID NO.: 20, SEQ ID NO.: 21, SEQ ID NO.: 22, SEQ ID NO.: 23, SEQ ID NO.: 62, SEQ ID NO.: 63, SEQ ID NO.: 64, SEQ ID NO.: 65, SEQ ID NO.: 66, SEQ ID NO.: 67, SEQ ID NO.: 68, SEQ ID NO.: 69, SEQ ID NO.: 70, SEQ ID NO.: 71 y combinaciones de las mismas.</i>	<i>Corresponde a la reivindicación 11 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.</i>
12. <i>El método de conformidad con la reivindicación 1, caracterizado porque dichos antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatona, colina, hidrocortisona, Vitamina C, Vitamina E o combinaciones de los mismos.</i>	15. <i>El método de conformidad con la reivindicación 18, caracterizado porque tales antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatona, colina, hidrocortisona, Vitamina C, Vitamina E o combinaciones de los mismos.</i>	<i>Corresponde a la reivindicación 12 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.</i>

13. El método de conformidad con la reivindicación 1, caracterizado porque la recolección tiene un color que es: a. no más amarillo-marrón que el Estándar Europeo de Color BY2; b. no más amarillo-marrón que el Estándar Europeo de Color BY3; c. no más amarillo-marrón que el Estándar Europeo de Color BY4; d. no más amarillo-marrón que el Estándar Europeo de Color BY5; e. entre el Estándar Europeo de Color BY2 y BY3; o f. entre el Estándar Europeo de Color BY2 y BY4, y en donde la concentración de aflibercept en la recolección es 5,0 g/L.	17. El método de conformidad con la reivindicación 18, caracterizado porque la recolección tiene un color que es: a. no más amarillo-marrón que el Estándar Europeo de Color BY2; b. no más amarillo-marrón que el Estándar Europeo de Color BY3; c. no más amarillo-marrón que el Estándar Europeo de Color BY4; d. no más amarillo-marrón que el Estándar Europeo de Color BY5; e. entre el Estándar Europeo de Color BY2 y BY3; o f. entre el Estándar Europeo de Color BY2 y BY4, y en donde la concentración de aflibercept en la recolección es 5,0 g/L.	Corresponde a la reivindicación 13 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.
14. El método de conformidad con la reivindicación 13, caracterizado porque el color de la recolección es caracterizado en el espacio de color L*, a*, b*, de CIE, donde L* es aproximadamente 70 hasta aproximadamente 99, a* es aproximadamente 0 y b* es aproximadamente 20 o menos de 20 cuando la concentración de aflibercept es 5,0 g/L.	16. El método de conformidad con la reivindicación 17, caracterizado porque el color de la recolección es caracterizado en el espacio de color L*, a*, b*, de CIE, donde L* es aproximadamente 70 hasta aproximadamente 99, a* es aproximadamente 0 y b* es aproximadamente 20 o menos de 20 cuando la concentración de aflibercept es 5,0 g/L.	Corresponde a la reivindicación 14 de la solicitud colombiana, en donde se ajustó la numeración y la dependencia.
15. Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende: (a) proporcionar una célula hospedera diseñada por ingeniería genética para expresar aflibercept; (b) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 μM o aproximadamente 0,4 μM y uno o más de los siguientes: i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 μM; ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 μM; iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 μM; iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM; y v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM a aproximadamente 10,0 mM para cualquier antioxidante único; y (c) recolectar el aflibercept producido por tal célula hospedera, donde el color de dicha cosecha es: a. no más amarillo-marrón que el Estándar Europeo de Color BY2; b. no más amarillo-marrón que el Estándar Europeo de Color BY3; c. no más amarillo-marrón que el Estándar Europeo de Color BY4; d. no más amarillo-marrón que el Estándar Europeo de Color BY5; e. entre el Estándar Europeo de Color BY2 y BY3; o	31. Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende: (a) proporcionar una célula hospedera diseñada por ingeniería genética para expresar aflibercept; (b) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 μM o aproximadamente 0,4 μM y uno o más de los siguientes: i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 μM; ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 μM; iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 μM; iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM; y v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para cualquier antioxidante único; y (c) recolectar el aflibercept producido por tal célula hospedera, en donde el color de tal recolección es a. no más amarillo-marrón que el Estándar Europeo de Color BY2; b. no más amarillo-marrón que el Estándar Europeo de Color BY3; c. no más amarillo-marrón que el Estándar Europeo de Color BY4; d. no más amarillo-marrón que el Estándar Europeo de Color BY5; e. entre el Estándar Europeo de Color BY2 y BY3; y/o	Corresponde a la reivindicación 15 de la solicitud colombiana.

<i>f. entre el Estándar Europeo de Color BY2 y BY4, y en donde la concentración de aflibercept en la recolección es 5,0 g/L.</i>	<i>f. entre el Estándar Europeo de Color BY2 y BY4, en donde la concentración de aflibercept es 5,0 g/L.</i>	
<i>16. Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende: (a) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 µM o aproximadamente 0,4 µM y uno o más de los siguientes; i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 µM; ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 µM; iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 µM; iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM; y v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para cualquier antioxidante único; y (b) recolectar el aflibercept producido por tal célula hospedera.</i>	<i>32. Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende: (a) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 µM o aproximadamente 0,4 µM y uno o más de los siguientes; i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 µM; ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 µM; iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 µM; iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM; y v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para cualquier antioxidante único; y (b) recolectar el aflibercept producido por tal célula hospedera.</i>	<i>Corresponde a la reivindicación 16 de la solicitud colombiana</i>



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/996,030	08/18/2020	Shawn Lawrence	070816-02250	3885
151431	7590	12/02/2020		
Kramer Levin Naftalis & Frankel LLP			EXAMINER	
1177 Avenue of the Americas			RAMIREZ, DELIA M	
New York, NY 10036				
			ART UNIT	PAPER NUMBER
			1652	
			NOTIFICATION DATE	DELIVERY MODE
			12/02/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

dtorniali@kramerlevin.com
jcaplan@kramerlevin.com
klpatent@kramerlevin.com

DETAILED ACTION

Status of the Application

Claims 1-30 are pending.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A preliminary amendment of claim 22, as submitted in a communication filed on 8/18/2020 is acknowledged.

Applicant's election with traverse of Group I, claims 2-30, drawn in part to a method of producing aflibercept with a CHO cell, the combination of variants of SEQ ID NO: 17-23, and a color no more yellow-brown than BY2, as submitted in a communication filed on 11/11/2020 is acknowledged.

Applicant's traverse is on the ground that the particular type of host cell should not require additional searches for a search of the claimed invention directed to the recited aflibercept variants, such as oxo-histidines and oxo-tryptophans. Applicant's arguments have been fully considered but are not persuasive to withdraw the restriction requirement. It would be erroneous to assume that literature that discloses a method practiced with CHO cells would also disclose the same method practiced with other types of cells, or that a method practiced with other cells would be an obvious variation of a method disclosed in the art which is practiced with CHO cells. Therefore, contrary to Applicant's assertions, a comprehensive search of all the inventions would require different keyword searches in the patent and non-patent literature. Thus, an examination of all the claimed inventions would impose an undue burden on the Office. As indicated in the prior Office action, the restriction requirement among the inventions is subject to the nonallowance of claim 1 (linking claim). Upon the indication of allowability of the linking claim, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise requiring all the limitations of the allowable linking claim will be rejoined and fully examined in accordance with 37 CFR 1.104.

The requirement is deemed proper and therefore is made FINAL.

Claims 1-8, 10-13, 15-16, 23-30 and claims 9, 14, 17, 18-22 in part are at issue and are being examined herein.

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claims are directed to a method of producing aflibercept. Appropriate correction is required.
2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See page 46, paragraph [0189], several instances. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 63/065,012 filed on 08/13/2020.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 11/25/2020 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

5. The drawings submitted on 8/18/2020 have been reviewed and are accepted by the Examiner for examination purposes.

Claim Objections

6. Claim 9 is objected to due to the recitation of “selected from a group consisting of...”. The term should be amended to recite “selected from the group consisting of...”. Appropriate correction is required.

Claim Rejections - 35 USC § 112(b) or Second Paragraph (pre-AIA)

7. The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

8. The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-30 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

10. Claim 1 (claims 2-17 dependent thereon) is indefinite in the recitation of “... aflibercept having a reduced amount of aflibercept variants” for the following reasons. It is unclear as to how a product (aflibercept) can have variants of itself. If the product has variants of itself, it is no longer the product but a mixture of a product and its variants. Furthermore, the term “reduced amount of...” is unclear absent a recitation of a reference point/condition to compare with (i.e., reduced compared to what). If the intended limitation is “a method of producing ..., wherein said method results in the production of a reduced amount of variants... compared to the amount of variants produced ...”, the claim should be amended accordingly. In addition, it is unclear from the specification if the term “aflibercept” as used in the claims is associated to a single amino acid sequence. In the absence of a sequence identifier associated with the term “aflibercept”, it is unclear as to what constitutes a variant of “aflibercept”, particularly if the term intends to encompass a genus of proteins and not a single one. For example, if the

term is intended to encompass more than a single protein, a protein comprising SEQ ID NO: X as well as a protein comprising SEQ ID NO: X minus the last 3 amino acids of the C-terminus can be considered to be “aflibercept”. If the term is intended to encompass a single protein, the protein comprising all of SEQ ID NO: X minus the last 3 amino acids of the C-terminus would be considered an “aflibercept variant”. A cursory review of US Patent No. 7,396,664 (common assignee Regeneron), discloses a protein comprising SEQ ID NO: 8. It may appear that this protein is related to “aflibercept”. Claim 1 of said patent refers to a genus of proteins that comprise amino acids 27-231 of SEQ ID NO: 8 and either amino acids 232-458, 232-457, 352-458, or 352-457 of SEQ ID NO: 8. Therefore, if SEQ ID NO: 8 in that patent is related to aflibercept, it appears that more than one protein can be considered to be “aflibercept” (e.g., variant that comprises amino acids 27-231, 352-458 of SEQ ID NO: 8, variant that comprises amino acids 27-457, amino acids 27-458 of SEQ ID NO: 8, variant that comprises amino acids 27-231, 352-457 of SEQ ID NO: 8). If the sequence identifier associated with “aflibercept” is disclosed in the specification, it is suggested the claim be amended to include the sequence identifier so that it is clear as to what constitutes an aflibercept variant (e.g., any protein that does not comprise SEQ ID NO: X).
Correction is required.

11. Claim 1 (claims 2-17 dependent thereon) is indefinite in the recitation of “wherein a target value of aflibercept variants is as follows: i. said target value is obtained...wherein the cumulative concentration of...in said CDM is...” for the following reasons. While the preamble prior to the limitations in (i)-(vi) refer to what a target value should be, the statements in (i)-(vi) are not values but rather concentrations of metal ions, cysteine, and anti-oxidants. In addition, it is unclear as to what a “target value of aflibercept variants” is within the context of the claim. There is no statement correlating the “reduced amount of aflibercept variants” with a “target value”. If the intended limitation is “wherein the reduced amount of... is obtained by (i) using a cumulative concentration of X in said CDM ...”, the claim should be amended accordingly. Correction is required.

12. Claims 1-8, 19, 21, 23, 25 (claims 9-17, 20, 22, 24, 26-30 dependent thereon) are indefinite in the recitation of “less than or equal to about X”, “no more than about”, and “less than about”, for the

following reasons. The term “about” encompasses a range which includes values which are higher and lower than the recited reference value. The term “less than” implies that only values less than the recited reference value are encompassed. The term “no more than” implies that only values equal or less to the reference value are encompassed. Therefore, in the absence of a clear definition of what is encompassed by the term “about”, the terms “less than about”, “less than or equal to about X” and “no more than about” are unclear and confusing since the terms refer to values which are (a) less, or (b) less or equal than undefined values which are either higher or lower than the recited reference values. In essence, the terms eliminate the relevance of the recited reference points because the reference values becomes variable and undefined. Correction is required.

13. Claim 2 is indefinite in the recitation of “...comprises less than...20% aflibercept variants” for the following reasons. The term “20% aflibercept variants” is unclear because one cannot determine which is the material where 20% of its components is made of aflibercept variants. Is 20% of all the protein produced by the method made of aflibercept variants? Furthermore, as explained above, the term “aflibercept variants” is unclear in the absence of a structural definition of “aflibercept” to distinguish it from variants. For examination purposes, no patentable weight will be given to the term. Correction is required.

14. Claim 10 is indefinite in the recitation of “wherein said clarified harvest comprises one or more...” because there is no antecedent basis for “the” clarified harvest in claim 1 or 10. For examination purposes, it will be assumed that the term recites “wherein said harvest comprises one or more...”. Correction is required.

15. Claims 16 and 18 (claims 19-22 dependent thereon) are indefinite in the recitation of “wherein said color is characterized in the CIE L*, a*, B* color space where L* is about 70 to about 99...” and “wherein, in the CIEL*, a*, b* color space is about...” for the following reasons. It appears from the teachings of the art that CIELAB colors are defined relative to the white point of the CIEXYZ space from which they were converted, and that they do not define absolute colors. See the attached Wikipedia article describing CIELAB (arrow). Therefore, in the absence of a value for a white point, claims 16 and

18 refer to a relative color. For examination purposes, no patentable weight will be given to the terms.

Claim 16 will be interpreted as a duplicate of claim 1. Correction is required.

16. Claims 16, 17, 18, 24, 26 (claims 19-22 dependent thereon) are indefinite in the recitation of “concentration of aflibercept is normalized to 5.0 g/l”, and “wherein the concentration of protein ... is normalized to 5.0 g/L” for the following reasons. It is unclear as to how a protein concentration is normalized to a particular concentration. The term “normalize” can have different meanings. For example, normalization can be the adjustment of values measured on different scales to a common scale. It can also be the multiplication of data by a factor that makes the norm or some associated quantity such as an integral equal to a desired value, usually 1. It appears from the specification that Applicant has used the protein concentration of 5 g/L as the protein concentration required to make a color measurement/color determination. Therefore, if the intended limitation in (a) claim 16 is “wherein the ... sample of (b) has a yellow-brown color... when the concentration of ... is 5 g/L”, (b) claim 17 is “wherein the color of the... sample of (b) at a concentration of 5 g/L is a. or f....”, (c) claim 18 is “wherein the color of said harvest when the concentration of ... is 5 g/L is a...b....c...”, (d) claim 26 is “when the concentration of ... in said harvest is 5 g/L”, the claims be amended accordingly. Correction is required.

17. Claim 17 is indefinite in the recitation of “... method of claim 1, wherein said yellow-brown of (b) color is..... clarified harvest...” because there is no antecedent basis in claim 1 for “yellow-brown” or “clarified” harvest. Claim 17 will be interpreted as a duplicate of claim 1. Correction is required.

18. Claims 17-18 (claims (claims 19-22 dependent thereon) are indefinite in the recitation of “European Color Standard BYx” for the following reasons. While the prior art discloses European Pharmacopeia color standards, it is unclear if the recited European standards are the same as the European Pharmacopeia color standards. If the intended standards are the European Pharmacopeia color standards, the claims should be amended accordingly. No patentable weight will be given to limitations regarding color. Correction is required.

19. Claim 18 (claims 19-22 dependent thereon) is indefinite in the recitation of “wherein the color of said harvest is characterized as follows: a. no more.....e. BY3; f. between European color.....” because it is unclear if the color is intended to be one that meets all of the limitations of a-f or if the color is one that meets at least one of a-f. Please note that there is no “and”/“or” between items e. and f. No patentable weight will be given to limitations regarding color. Correction is required.

20. Claim 19 (claims 20-22 dependent thereon) is indefinite in the recitation of “wherein said harvest having a certain target BY value” because there is no antecedent basis for a target BY value. No patentable weight will be given to the phrase. Correction is required.

21. Claim 19 (claims 20-22 dependent thereon) is indefinite in the recitation of “the cumulative concentration of X in said CDM to less than... μM ” for the following reasons. The phrase appears to be incomplete. As written, it is unclear as to the relationship between “the concentration of X” and the term “less than...”. Is the concentration reduced/increased to less than a particular value? Is the concentration less than a particular value? If the intended limitation is “wherein said harvest has X color when said CDM has (i) a concentration of X which is less than..., (ii) a concentration of Y which is less than...”, the claim should be amended accordingly. Correction is required.

22. Claim 22 is indefinite in the recitation of “wherein decreasing metal concentration in said CDM to 0.5x reduced color with increase in titer ...” for the following reasons. There is no antecedent basis for a titer in claim 19. Furthermore, there is nothing indicating the specific compound associated with the titer being referred to (titer of what). In addition, the term “0.5x” is unclear because there is no definition of the amount/concentration associated with “X” so that one could determine a decrease (i.e., which is the metal concentration reduced to half). For examination purposes, claim 22 will be interpreted as a duplicate of claim 19. Correction is required.

23. Claim 23 (claims 24-30 dependent thereon) is indefinite in the recitation of “...the cumulative concentration of X in said CDM to less than... μM ..” for the following reasons. The phrase appears to be incomplete. As written, it is unclear as to the relationship between “the concentration of X” and the term “less than...”. Is the concentration reduced/increased to less than a particular value? Is the concentration

less than a particular value? If the intended limitation is “wherein (i) the.... concentration of X in said CDM is less than.....”, the claim should be amended accordingly. Correction is required.

24. Claim 23 (claims 24-30 dependent thereon) is indefinite in the recitation of “forming a harvest comprising aflibercept wherein:...(vi) including one or more anti-oxidant in said CDM in a concentration of....” for the following reasons. The term “wherein ..(vi) including one or more....” is unclear and confusing. If the intended limitation is “wherein(vi) said CDM comprises one or more anti-oxidants in a concentration....”, the claim should be amended accordingly. Correction is required.

25. Claim 24 is indefinite in the recitation of “titer of said aflibercept is increased.. while said sample color does not increase....” for the following reasons. The term is unclear in the absence of a reference to compare with and determine whether there is an increase in titer. In addition, the term “...color does not increase...” is unclear because while a color can change, colors do not increase or decrease. For examination purposes, claim 24 will be interpreted as a duplicate of claim 23. Correction is required.

26. Claim 26 (claims 24-30 dependent thereon) is indefinite in the recitation of “wherein said sample color BY value is greater than about BY3” for the following reasons. There is no antecedent basis for a sample color BY in claim 24. Furthermore, even if the term “BY3” is intended to be a well-defined color, it is unclear as to how one could determine what is the limitation intended by the phrase “greater than about BY3” when colors cannot be greater than another color. Moreover, a color cannot be “about” color X. For example, the color of a sample cannot be about brown. Colors are not values. For examination purposes, claim 26 will be assumed to be a duplicate of claim 23. Correction is required.

27. Claim 27 is indefinite in the recitation of “wherein said sample color has a “b*” value that is reduced by about 45% compared to aflibercept cultured in said CDM where concentration of (i) to (vi) are not maintained” for the following reasons. It is unclear as to what a “b*” value is and there is no reference or definition of what a “b*” value is in claim 23, from which claim 27 depends. Furthermore, it is unclear as to which concentration of (i) to (vi) has to be maintained. Even if one assumes that items i.-vi. in claim 23 are concentrations of different metal ions, anti-oxidants, and cysteine in the CDM, items i.-vi. refer in part to concentrations that are less than or equal to value X. Thus, it is unclear if the term

“concentrations ...not maintained” refers to not maintaining the concentration of the different metal ions, anti-oxidants, and cysteine in the CDM at value X, or not maintaining the concentration of the different metal ions, anti-oxidants and cysteine in the CDM at values which are less or equal to value X. In addition, the term “wherein said sample color has a b* value that is reduced...compared to aflibercept..” is unclear because (i) aflibercept is not a cell, thus it cannot be “cultured”, and (ii) even if the intended term is “aflibercept obtained by culturing a host cell that produces it”, one cannot determine if the intended comparison is with a “b*” value associated with aflibercept obtained by culturing a host cell under a particular set of conditions. For examination purposes, claim 27 will be assumed to be a duplicate of claim 23. Correction is required.

28. Claim 30 is indefinite in the recitation of “minimal impact to titer” for the following reasons. The term “minimal” is a relative term not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In addition, there is no indication as to which is the product associated with the term “titer” (i.e., titer of what). For examination purposes, claim 30 will be interpreted as a duplicate of claim 23. Correction is required.

29. When amending the claims, applicant is advised to carefully review all examined claims and make the necessary changes to ensure proper antecedent basis and dependency.

Claim Rejections - 35 USC § 102 (AIA)

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

31. Claims 1-30 are rejected under 35 U.S.C. 102(a)(1) and 102(a)(2) as being anticipated by Johnson et al. (US Publication No. 2018/0223249 published 8/9/2018) as evidenced by Daly et al. (US Patent No. 7,396,664, issued 7/8/2008).

Claims 1-17 are directed in part to a method of producing aflibercept by culturing a CHO host cell that expresses aflibercept in a chemically defined medium (CDM), wherein said method also produces variants of aflibercept that result from oxidation of one or more amino acid residues selected from methionine, tryptophan, histidine, phenylalanine, and tyrosine, wherein the CDM comprises an anti-oxidant, including taurine, at a concentration of between 0.001 mM to 10 mM, wherein said aflibercept variant comprises the amino acid sequences of SEQ ID NO: 17-23. Claims 18-22 are directed in part to a method of producing aflibercept produced by a host cell that expresses aflibercept, wherein said host cell is cultured in a CDM that comprises an anti-oxidant, including taurine, wherein the concentration of the ant-oxidant is between 0.001 mM to 10 mM. Claims 23-30 are directed in part to a method of increasing the production of aflibercept harvested from culturing a host cell that expresses aflibercept, wherein the host cell is cultured in a CDM that comprises an anti-oxidant, including taurine, at a concentration between 0.001 mM to 10 mM, and wherein said CDM also comprises uridine. See Claim Rejections - 35 USC § 112(b) or Second Paragraph (pre-AIA) for claim interpretation. Please note that the concentrations recited in claims 1, 3-7, 19, 23 are recited in the alternative so the CDM is only required to have one of the concentrations recited.

Johnson et al. teach a method of producing proteins of interest, including aflibercept (page 11, paragraph [0106], right column), wherein said method comprises culturing a CHO cell, an embryonic kidney 293 cell, a BHK cell (page 11, right column, paragraph [0107]), an SP2/0 cell or an NS-0 cell (page 5, right column, paragraph [0051]) that expresses said protein of interest, wherein said culturing is carried out in a chemically defined medium (Abstract, page 6, right column, paragraph [0059]) that comprises taurine at a concentration of 0.1-10 mM (page 7, left column, paragraph [0063]), nucleosides such as uridine (page 7, right column, paragraph [0069]), and cysteine at a concentration of 1.1 mM (page

2, Table 1). Johnson et al. teach that the addition of taurine increases the titer of the desired protein (Abstract; page 1, paragraph [0005]). Johnson et al. teach that aflibercept is a VEGF trap (page 11, right column, line 8) which in the absence of evidenced to the contrary, comprises SEQ ID NO: 8 as disclosed by Daly et al. The polypeptide of SEQ ID NO: 8 comprises SEQ ID NO: 17-23 as shown in the alignments below. Therefore, in the absence of evidence to the contrary, the aflibercept of Johnson et al. comprises SEQ ID NO: 17-23. The specification of the instant application asserts that culturing host cells that express aflibercept in CDM that comprises an antioxidant such as taurine at a concentration of 0.001 mM to 10 mM results in a reduction in the amount of aflibercept having oxidized amino acids, wherein said amino acids are selected from methionine, tryptophan, histidine, phenylalanine, and tyrosine. The specification of the instant application also asserts that one could increase the titer of aflibercept by culturing a host cell that expresses aflibercept in a CDM that comprises an anti-oxidant such as taurine at a concentration of 0.001 mM to 10 mM. Therefore, it follows that the method of Johnson et al. would inherently result in the recited reduction of aflibercept comprising oxidized amino acids and an increase in aflibercept titers. As such, the method of Johnson et al. anticipate the instant claims as written/interpreted.

Query = SEQ ID NO:8
Sbjct = SEQ ID NO:17

NW Score	Identities	Positives	Gaps
-366	16/458 (3%)	16/458 (3%)	442/458 (96%)

Query	1	MVS YWDTGVL LCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS	60
Query	61	PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT	120
Query	121	HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD	180
Query	181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC	240
Sbjct	1	DKTHTCPPC	9
Query	241	PAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT	300
Sbjct	10	PAPELLG	16
Query	301	KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY	360
Query	361	TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSK	420

Query 421 LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK 458

Query = SEQ ID NO:8
Sbjct = SEQ ID NO:18

NW Score	Identities	Positives	Gaps
-372	17/458 (4%)	17/458 (3%)	441/458 (96%)

Query 1 MVS YWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS 60

Query 61 PNITVTLKKFPLDTLIPDGKRIIWD SRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT 120

	EIGLLTCEATVNGHLYK	
Sbjct 1	EIGLLTCEATVNGHLYK	17

Query 121 HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD 180

Query 181 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKHTHTCPPC 240

Query 241 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300

Query 301 KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360

Query 361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK 420

Query 421 LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK 458

Query = SEQ ID NO:8
Sbjct = SEQ ID NO:19

NW Score	Identities	Positives	Gaps
-344	23/458 (5%)	23/458 (5%)	435/458 (94%)

Query 1 MVS YWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS 60

Query 61 PNITVTLKKFPLDTLIPDGKRIIWD SRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT 120

Query 121 HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD 180

	QTNTIIDVVLSPSHGIELSVGEK	
Sbjct 1	QTNTIIDVVLSPSHGIELSVGEK	23

Query 181 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKHTHTCPPC 240

Query 241 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300

Query 301 KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360

Query 361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK 420

Query 421 LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK 458

Query = SEQ ID NO:8
Sbjct = SEQ ID NO:20

NW Score	Identities	Positives	Gaps
-338	21/458 (5%)	21/458 (4%)	437/458 (95%)
Query 1	MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS	60	
Query 61	PNITVTLKKFPLDTLIPDGKRIIWDSSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT	120	
Query 121	HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD	180	
Sbjct 1	TELVGIDFNWEYPSSKHQHK	21	
Query 181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKHTHTCPPC	240	
Query 241	PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT	300	
Query 301	KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY	360	
Query 361	TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK	420	
Query 421	LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK	458	

Query = SEQ ID NO:8
Sbjct = SEQ ID NO:21

NW Score	Identities	Positives	Gaps
-433	7/458 (2%)	7/458 (1%)	451/458 (98%)
Query 1	MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS	60	
Query 61	PNITVTLKKFPLDTLIPDGKRIIWDSSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT	120	
Sbjct 1	TNYLT	5	
Query 121	HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD	180	
Sbjct 6	HR	7	
Query 181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKHTHTCPPC	240	
Query 241	PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT	300	
Query 301	KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY	360	
Query 361	TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK	420	
Query 421	LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK	458	

Query = SEQ ID NO:8
Sbjct = SEQ ID NO:22

NW Score	Identities	Positives	Gaps
-329	24/458 (5%)	24/458 (5%)	434/458 (94%)

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Query 1  MVS YWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS 60
          SDTGRPFVEMYSEIPEIIHMTGR
Sbjct 1  SDTGRPFVEMYSEIPEIIHMTGR 24

Query 61  PNITVTLKKFPLDTLIPDGKRIIWD SRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT 120

Query 121 HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD 180

Query 181 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC 240

Query 241 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300

Query 301 KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360

Query 361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK 420

Query 421 LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK 458

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Query = SEQ ID NO:8
Sbjct = SEQ ID NO:23

NW Score	Identities	Positives	Gaps
-441	6/458 (1%)	6/458 (1%)	452/458 (98%)

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Query 1  MVS YWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS 60

Query 61  PNITVTLKKFPLDTLIPDGKRIIWD SRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT 120

Query 121 HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELVGIDFNWEYPSSKHQHKLVNRD 180

Query 181 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC 240
          VHEKDK
Sbjct 1  VHEKDK 6

Query 241 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300

Query 301 KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360

Query 361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK 420

Query 421 LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK 458

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32. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103 (AIA)

33. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

34. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

35. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

36. Claims 1-30 are rejected under 35 U.S.C. 103 as being unpatentable over Johnson et al. (US Publication No. 2018/0223249 published 8/9/2018) as evidenced by Daly et al. (US Patent No. 7,396,664, issued 7/8/2008) in view of Vijayasankaran et al. (US Publication No. 2013/0281355 published 10/24/2013).

The teachings of Johnson et al. and Daly et al. have been discussed above. Neither Johnson et al. nor Daly et al. teach methods to improve quality properties of the desired protein such as lower color intensities. Vijayasankaran et al. teach a method to produce a protein of interest by culturing a host cell that expresses said protein in a chemically defined medium to lower color intensity while maintaining the

product yield (page 1, paragraph [0007]). Vijayasankaran et al. teach that their media components are capable of providing a polypeptide drug product with acceptable quality attributes, such as an acceptable color for therapeutic use (page 9, paragraph [0071]). Vijayasankaran et al. teach that their chemically defined medium comprises iron in the form of ferric citrate or ferrous sulfate at a concentration of about 2 μM to about 50 μM and hydrocortisone at a concentration of about 0.5 μM (page 13, Table 1).

Vijayasankaran et al. teach that their method uses mammalian cells as host cells, wherein said mammalian cells are CHO cells, human embryonic kidney cells, or BHK cells (page 17, paragraph [0094]).

Vijayasankaran et al. teach that proteins that can be made with their method are receptors for growth factors (page 18, paragraph [0103]) as well as antibodies (page 18, paragraph [0104]). Vijayasankaran et al. teach that by using ferric citrate so that the iron concentration is between 10-20 μM results in the lowest color index number (Figure 12A). Vijayasankaran et al. do not teach aflibercept.

Claims 1-17 are directed in part to a method of producing aflibercept by culturing a CHO host cell that expresses aflibercept in a chemically defined medium (CDM), wherein said method also produces variants of aflibercept that result from oxidation of one or more amino acid residues selected from methionine, tryptophan, histidine, phenylalanine, and tyrosine, wherein the CDM comprises (i) iron at a concentration of less than 55 μM , and (ii) one or more anti-oxidants, including taurine and hydrocortisone, at a concentration of about 0.001 mM to about 10 mM, wherein said aflibercept variant comprises the amino acid sequences of SEQ ID NO: 17-23. Claims 18-22 are directed in part to a method of producing aflibercept produced by a host cell that expresses aflibercept, wherein said host cell is cultured in a CDM that comprises iron at a concentration that is less than 55 μM , and one or more anti-oxidants, including taurine and hydrocortisone, wherein the concentration of the ant-oxidant is about 0.001 mM to about 10 mM. Claims 23-30 are directed in part to a method of increasing the production of aflibercept harvested from culturing a host cell that expresses aflibercept, wherein the host cell is cultured in a CDM that comprises iron at a concentration of less than 55 μM and one or more anti-oxidants, including taurine and hydrocortisone, at a concentration of about 0.001 mM to about 10 mM, and wherein said CDM also comprises uridine. See Claim Rejections - 35 USC § 112(b) or Second Paragraph (pre-

AIA) for claim interpretation. Please note that the concentrations recited in claims 1, 3-7, 19, 23 are recited in the alternative so the CDM is only required to have one of the concentrations recited.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to further add iron and hydrocortisone at the recited concentrations to the CDM medium used in the method of Johnson et al. A person of ordinary skill in the art is motivated to further add iron at a concentration of less than 55 μM (e.g., 10 μM , 20 μM , 50 μM) and hydrocortisone at a concentration of about 1 μM (e.g., 0.5 μM) to lower color intensity and improve the quality of aflibercept. One of ordinary skill in the art has a reasonable expectation of success at adding iron and hydrocortisone at the recited concentrations and obtain a product with lower color intensities because Vijayasankaran et al. teach that lower color intensity is obtained when CDM that comprises iron and hydrocortisone at the recited concentrations is used. It should also be noted that the specification asserts that the presence of an anti-oxidant such as taurine at the recited concentrations result in an aflibercept solution that is more yellow than brown. Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention.

Conclusion

37. No claim is in condition for allowance.

38. Information regarding the status of an application 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>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

39. Applicant is advised that any Internet email communication by the Examiner has to be authorized by Applicant in written form. See MPEP § 502.03 (II). Without a written authorization by Applicant in place, the USPTO will not respond via Internet email to any Internet correspondence which

contains information subject to the confidentiality requirement as set forth in 35 U.S.C. 122. Sample written authorization language can be found in MPEP § 502.03 (II). An Authorization for Internet Communications in a Patent Application or Request to Withdraw Authorization for Internet Communications form (SB/439) can be found at <https://www.uspto.gov/patent/forms/forms-patent-applications-filed-or-after-september-16-2012>, which can be electronically filed.

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DELIA M RAMIREZ, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (408) 918-7584. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/DELIA M RAMIREZ/
Primary Examiner, Art Unit 1652

DR\
November 27, 2020

<i>Notice of References Cited</i>	Application/Control No. 16/996,030		Applicant(s)/Patent Under Reexamination Lawrence et al.	
	Examiner DELIA M RAMIREZ		Art Unit 1652	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20180223249-A1	08-2018	JOHNSON; Amy S.	C12N5/0018	1/1
*	B	US-7396664-B2	07-2008	Daly; Thomas J.	C07K14/71	424/134.1
*	C	US-20130281355-A1	10-2013	VIJAYASANKARAN; Natarajan	C12N5/005	514/1.1
	D					
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	N					
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	R					
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	T					

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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	W	
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

CPC - Searched*		
Symbol	Date	Examiner
C07K14/71; C12P21/02; C07K2319/30	11/27/2020	DR

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STN- index bioscience medicine - see search history and entire transcript	11/27/2020	DR
WEST- USPT, PGPB, DWPI, EPAB, JPAB- see search history	11/27/2020	DR
PALM- inventor search-Shawn Lawrence, Amy Johnson, Meghan Casey, Jaimie Mastrogiacono, Shunhai Wang, Ning Li	11/27/2020	
parent cases considered-63/065,012	11/27/2020	DR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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<i>Index of Claims</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	10/10/2020	11/22/2020							
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	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	✓							
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and TEMA Add Numeric Property Search
NEWS 22 OCT 7 EP Appeal Data from European Patent Register Added to
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31	FILE AGRICOLA
48	FILE BIOSIS
105	FILE BIOTECHABS
105	FILE BIOTECHDS
42	FILE BIOTECHNO
30	FILE CABA
75	FILE CAPLUS
10	FILE CEABA
29	FILE DDFU
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54	FILE DRUGU
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109	FILE ESBIODBASE
14	FILE FSTA
4	FILE GENBANK

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644	FILE USPAT2
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F7	105	BIOTECHABS
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F9	83	PQSCITECH
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F15	45	MEDLINE
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F17	42	BIOTECHNO

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F22	10	CEABA
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L2 3775 (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (COLO
R? OR COLOU?)

=> s l2(s)(iron? or ferrou? or ferric? or zinc? or "zn" or coppe? or "cu" or nicke?
or "ni" or cystein? or "cys" or "anti-oxidant")

L3 304 L2(S)(IRON? OR FERROU? OR FERRIC? OR ZINC? OR "ZN" OR COPPE?
OR "CU" OR NICKE? OR "NI" OR CYSTEIN? OR "CYS" OR "ANTI-OXIDANT"
)

=> s l3(s)((media? or medium?) (20a)(define?))

L4 14 L3(S)((MEDIA? OR MEDIUM?) (20A)(DEFINE?))

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L5 ANSWER 1 OF 14 USPAT2 on STN

ACCESSION NUMBER: 2019:166288 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods
for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,
UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED
STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10829732	B2	20201110
APPLICATION INFO.:	US 2018-16151904		20181004 (16)
RELATED APPLN. INFO.:	Division of Ser. No. US 2015-14852311, filed on 11 Sep 2015, Pat. No. US 10131873 Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	22	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 11 Drawing Page(s)	
LINE COUNT:	4261	

AB Cell culture media comprising antioxidants are provided herein as are
methods of using the media for cell culturing and polypeptide production
from cells. Compositions comprising polypeptides, such as therapeutic
polypeptides, produced by the methods herein are also provided.

L5 ANSWER 2 OF 14 USPAT2 on STN

ACCESSION NUMBER: 2019:3991 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods
for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,

PATENT ASSIGNEE(S): UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES
Genentech, Inc., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10676710	B2	20200609
APPLICATION INFO.:	US 2018-15997342		20180604 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14211416, filed on 14 Mar 2014, Pat. No. US 10017732		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	32	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)	
LINE COUNT:	4173	

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

L5 ANSWER 3 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2019:166288 USPATFULL Full-text
TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS FOR POLYPEPTIDE PRODUCTION
INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA, UNITED STATES
MEIER, Steven J., South San Francisco, CA, UNITED STATES
VARMA, Sharat, South San Francisco, CA, UNITED STATES
YANG, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190144817	A1	20190516
	US 10829732	B2	20201110
APPLICATION INFO.:	US 2018-16151904	A1	20181004 (16)
RELATED APPLN. INFO.:	Division of Ser. No. US 2015-14852311, filed on 11 Sep 2015, Pat. No. US 10131873 Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	27	
EXEMPLARY CLAIM:	1-64	
NUMBER OF DRAWINGS:	11 Drawing Page(s)	
LINE COUNT:	3948	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 14 USPATFULL on STN
 ACCESSION NUMBER: 2019:3991 USPATFULL Full-text
 TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS
 FOR POLYPEPTIDE PRODUCTION
 INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA,
 UNITED STATES
 MEIER, Steven J., South San Francisco, CA, UNITED
 STATES
 VARMA, Sharat, South San Francisco, CA, UNITED STATES
 YANG, Yi, South San Francisco, CA, UNITED STATES
 PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190002822	A1	20190103
	US 10676710	B2	20200609
APPLICATION INFO.:	US 2018-15997342	A1	20180604 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14211416, filed on 14 Mar 2014, Pat. No. US 10017732		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	37	
EXEMPLARY CLAIM:	1-63	
NUMBER OF DRAWINGS:	9 Drawing Page(s)	
LINE COUNT:	3852	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are
 methods of using the media for cell culturing and polypeptide production
 from cells. Compositions comprising polypeptides, such as therapeutic
 polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 14 USPAT2 on STN
 ACCESSION NUMBER: 2016:3643 USPAT2 Full-text
 TITLE: Cell culture compositions with antioxidants and methods
 for polypeptide production
 INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,
 UNITED STATES
 Meier, Steven J., South San Francisco, CA, UNITED
 STATES
 Varma, Sharat, South San Francisco, CA, UNITED STATES
 Yang, Yi, South San Francisco, CA, UNITED STATES
 PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10131873	B2	20181120
APPLICATION INFO.:	US 2015-14852311		20150911 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 11 Drawing Page(s)	
LINE COUNT:	4275	

AB Cell culture media comprising antioxidants are provided herein as are

methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

L5 ANSWER 6 OF 14 USPAT2 on STN

ACCESSION NUMBER: 2014:352125 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA, UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10017732	B2	20180710
APPLICATION INFO.:	US 2014-14211416		20140314 (14)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	24	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)	
LINE COUNT:	4101	

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

L5 ANSWER 7 OF 14 USPATFULL on STN

ACCESSION NUMBER: 2016:3643 USPATFULL Full-text
TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS FOR POLYPEPTIDE PRODUCTION
INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA, UNITED STATES
MEIER, Steven J., South San Francisco, CA, UNITED STATES
VARMA, Sharat, South San Francisco, CA, UNITED STATES
YANG, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160002593	A1	20160107
	US 10131873	B2	20181120
APPLICATION INFO.:	US 2015-14852311	A1	20150911 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	101	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	11 Drawing Page(s)	
LINE COUNT:	4302	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 14 USPATFULL on STN

ACCESSION NUMBER: 2014:352125 USPATFULL Full-text
TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS FOR POLYPEPTIDE PRODUCTION
INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA, UNITED STATES
MEIER, Steven J., South San Francisco, CA, UNITED STATES
VARMA, Sharat, South San Francisco, CA, UNITED STATES
YANG, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140314779	A1	20141023
	US 10017732	B2	20180710
APPLICATION INFO.:	US 2014-14211416	A1	20140314 (14)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	66	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Page(s)	
LINE COUNT:	3940	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 9 OF 14 USPATFULL on STN

ACCESSION NUMBER: 2014:291227 USPATFULL Full-text
TITLE: Process for the Production of Fine Chemicals
INVENTOR(S): Plesch, Gunnar, Potsdam, GERMANY, FEDERAL REPUBLIC OF
Blau, Astrid, Stahnsdorf, GERMANY, FEDERAL REPUBLIC OF
Herold, Michael Manfred, Berlin, GERMANY, FEDERAL REPUBLIC OF
Kamlage, Beate, Berlin, GERMANY, FEDERAL REPUBLIC OF
Wendel, Birgit, Berlin, GERMANY, FEDERAL REPUBLIC OF
Puzio, Piotr, Mariakerke (Gent), BELGIUM
Henkes, Stefan, Potsdam, GERMANY, FEDERAL REPUBLIC OF
Haake, Volker, Berlin, GERMANY, FEDERAL REPUBLIC OF
Van Camp, Wim, Sint-Denijs-Westrem, BELGIUM
Fahnenstich, Holger, Berlin, GERMANY, FEDERAL REPUBLIC OF
McKersie, Bryan, Raleigh, NC, UNITED STATES
Bruce, Wesley, Raleigh, NC, UNITED STATES
Christiansen, Nicole, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): BASF Plant Science Company GmbH, Ludwigshafen, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140259212	A1	20140911
APPLICATION INFO.:	US 2012-13510783	A1	20101118 (13)

WO 2010-EP6988

20101118

20120518 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2009-14472	20091118
	EP 2009-176396	20091118
	EP 2009-181052	20091222
	EP 2010-186930	20101008
	EP 2010-188863	20101026
	EP 2010-189169	20101028
	EP 2010-189358	20101029
	EP 2010-189943	20101104
	EP 2010-190115	20101105
	EP 2010-190348	20101108
	EP 2010-190441	20101109
	EP 2010-190649	20101110
	EP 2010-190780	20101111
	EP 2010-190795	20101111
	EP 2010-190934	20101112
	EP 2010-190974	20101112
	EP 2010-191021	20101112
	EP 2010-191126	20101115
	EP 2010-191238	20101115
	EP 2010-191282	20101116

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1-23
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 672727

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a process for the production of a fine chemical in a non-human organism, like a microorganism, a plant cell, a plant, a plant tissue or in one or more parts thereof. The invention furthermore relates to nucleic acid molecules, polypeptides, nucleic acid constructs, expression cassettes, vectors, antibodies, host cells, plant tissue, propagation material, harvested material, plants, microorganisms as well as agricultural compositions and to their use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2020 ACS on STN

ACCESSION NUMBER: 2014:376253 CAPLUS Full-text

TITLE: Iron mediated tryptophan oxidation and vitamin B12 carryover caused a brown color formation of protein drug substance manufactured in CHO cells using chemically defined media

AUTHOR(S): Xu, Jianlin; Jin, Mi; Song, Hangtian; Huang, Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger, Kirby; Lewen, Nancy S.; Tao, Li; Li, Zheng Jian

CORPORATE SOURCE: 1Biologics Process Development, Bristol-Myers Squibb Company, USA

SOURCE: Abstracts of Papers, 247th ACS National Meeting & Exposition, Dallas, TX, United States, March 16-20, 2014 (2014), BIOT-385. American Chemical Society: Washington, D. C.
CODEN: 69SHSU

DOCUMENT TYPE: Conference; Meeting Abstract; (online computer file)

LANGUAGE: English

AB Drug substance (DS) color is an important quality attribute for release, stability and comparability studies of therapeutic proteins. With the increase of DS concns. and biologics pipelines made in chem. defined media, atypical DS color other than colorless or pale yellow has been recently reported in the biopharmaceutical industry. This presentation reports an investigative approach to elucidate the root cause of a brown colored drug substance obsd. in manufg. using CHO cells. Although anal. characterization data indicated that the brown color DS had no major quality issue, it is necessary to find the root cause and reduce DS color to ease placebo design for clin. use. It was demonstrated that the brown color was caused by the chem. defined medium contg. high levels of iron,

vitamin B12 (VB12), and copper regardless of cell lines. Iron caused tryptophan oxidn. in the protein to form N-formylkynurenine and kynurenine products, which likely contributed to a yellow DS color. A pink DS color was caused by the residual VB12 bound to DS. The brown color was the result of the combinatory effect of yellow and pink colors. In addn., high levels of iron in the basal medium promoted cell growth and protein titer, while high levels of VB12 had no impact on cell culture performance. Copper neither caused any DS color nor improved titer. Finally a modified basal medium was developed to produce a pale yellow DS in manufg. To our knowledge, this study advances knowledge of the mechanism of DS color formation and cell culture manufg. processes for therapeutic proteins.

L5 ANSWER 11 OF 14 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2015:238056 BIOSIS Full-text
DOCUMENT NUMBER: PREV201500238056
TITLE: Iron mediated tryptophan oxidation and vitamin B12
carryover caused a brown color formation of protein drug
substance manufactured in CHO cells using chemically
defined media.
AUTHOR(S): Xu, Jianlin [Reprint Author]; Jin, Mi; Song, Hangtian;
Huang, Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger,
Kirby; Lewen, Nancy S.; Tao, Li; Li, Zheng Jian
CORPORATE SOURCE: Bristol Myers Squibb Co, Proc Dev 1Biol, New York, NY 10154
USA
jianlin.xu@bms.com
SOURCE: Abstracts of Papers American Chemical Society, (MAR 16
2014) Vol. 247, pp. 385-BIOT.
Meeting Info.: 247th National Spring Meeting of the
American-Chemical-Society (ACS). Dallas, TX, USA. March 16
-20, 2014. Amer Chem Soc.
CODEN: ACSRAL. ISSN: 0065-7727.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Mar 2015
Last Updated on STN: 18 Mar 2015

L5 ANSWER 12 OF 14 SCISEARCH COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2015:271312 SCISEARCH Full-text
THE GENUINE ARTICLE: AZ8HD
TITLE: Iron mediated tryptophan oxidation and vitamin B12
carryover caused a brown color formation of protein drug
substance manufactured in CHO cells using chemically
defined media
AUTHOR: Xu, Jianlin (Reprint); Jin, Mi; Song, Hangtian; Huang,
Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger,
Kirby; Tao, Li; Li, Zheng Jian
CORPORATE SOURCE: Bristol Myers Squibb Co, Proc Dev 1Biol, New York, NY
10154 USA
E-mail: jianlin.xu@bms.com
AUTHOR: Lewen, Nancy S.
CORPORATE SOURCE: Bristol Myers Squibb Co, Pharmaceut Dev, New York, NY
10154 USA
COUNTRY OF AUTHOR: USA
SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (16
MAR 2014) Vol. 247. MA 385-BIOT.
ISSN: 0065-7727.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036
USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 23 Feb 2015
Last Updated on STN: 23 Feb 2015

L5 ANSWER 13 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2012:179338 USPATFULL Full-text
TITLE: HCMV-related nucleic acids and microRNA

INVENTOR(S): Bentwich, Itzhak, Kfar Daniel, ISRAEL
PATENT ASSIGNEE(S): Rosetta Genomics, Inc., Rehovot, ISRAEL (non-U.S.
corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 8207316	B1	20120626
APPLICATION INFO.:	US 2003-707003		20031030 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2003-604984, filed on 29 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2002-303778, filed on 26 Nov 2002, ABANDONED Continuation-in-part of Ser. No. US 2002-310188, filed on 5 Dec 2002, ABANDONED Continuation-in-part of Ser. No. US 2003-604945, filed on 27 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2003-604942, filed on 28 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2003-604943, filed on 28 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2003-604944, filed on 28 Aug 2003, Pat. No. US 7217807 Continuation-in-part of Ser. No. US 2003-605838, filed on 30 Oct 2003, ABANDONED Continuation-in-part of Ser. No. US 2003-605840, filed on 30 Oct 2003, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-60457788	20030327 (60)
	US 2003-60441241	20030117 (60)
	US 2003-60411230	20030117 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Angell, J. E	
ASSISTANT EXAMINER:	Shin, Dana	
LEGAL REPRESENTATIVE:	Scott, Jr., Teddy, Polsinelli Shughart	
NUMBER OF CLAIMS:	4	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	26 Drawing Figure(s); 17 Drawing Page(s)	
LINE COUNT:	1069089	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a group of noel viral RNA regulatory genes, here identified as "viral genomic address messenger genes" or "VGAM genes", and as "Viral genomic record" or "VGR genes". VGAM genes selectively inhibit translation of known host target genes, and are believed to represent a pervasive viral attack mechanism. VGR genes encode an "operon"-like cluster of VGAM genes. VGAM and viral VGR genes may therefore be useful in diagnosing, preventing and treating viral disease. Several nucleic acid molecules are provided respectively encoding several VGAM genes, as are vectors and probes, both comprising the nucleic acid molecules, and methods and systems for detecting VGAM genes, and for counteracting their activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 14 OF 14 USPATFULL on STN

ACCESSION NUMBER: 2004:25211 USPATFULL Full-text
TITLE: Combination of an allosteric carboxylic inhibitor of matrix metalloproteinase-13 with celecoxib or valdecoxib
INVENTOR(S): Roark, William Howard, Ann Arbor, MI, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040019053	A1	20040129
APPLICATION INFO.:	US 2003-619662	A1	20030715 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-60396903	20020717 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	WARNER-LAMBERT COMPANY, 2800 PLYMOUTH RD, ANN ARBOR, MI, 48105	

NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: No Drawings
LINE COUNT: 8040

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a combination, comprising an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with celecoxib, or a pharmaceutically acceptable salt thereof, or valdecoxib, or a pharmaceutically acceptable salt thereof. This invention also provides a method of treating a disease that is responsive to inhibition of MMP-13 and cyclooxygenase-2, comprising administering to a patient suffering from such a disease the invention combination comprising an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with celecoxib, or a pharmaceutically acceptable salt thereof, or valdecoxib, or a pharmaceutically acceptable salt thereof. This invention also provides a pharmaceutical composition, comprising the invention combination comprising an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with celecoxib, or a pharmaceutically acceptable salt thereof, or valdecoxib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

The invention combination may also be further combined with other pharmaceutical agents depending on the disease being treated.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA, CIN, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGU, EMBASE, ESBIODASE, FSTA, GENBANK, IFIALL, IMSRESEARCH, KOSMET, MEDLINE, NTIS, ...' ENTERED AT 22:32:33 ON 27 NOV 2020

SEA (("CHO" (10A)CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (

121 FILE ADISCTI
6 FILE ADISINSIGHT
31 FILE AGRICOLA
48 FILE BIOSIS
105 FILE BIOTECHABS
105 FILE BIOTECHDS
42 FILE BIOTECHNO
30 FILE CABA
75 FILE CAPLUS
10 FILE CEABA
29 FILE DDFU
312 FILE DGENE
54 FILE DRUGU
60 FILE EMBASE
109 FILE ESBIODASE
14 FILE FSTA
4 FILE GENBANK
850 FILE IFIALL
1 FILE IMSRESEARCH
1 FILE KOSMET
45 FILE MEDLINE
1 FILE NTIS
83 FILE PQSCITECH
45 FILE SCISEARCH
61 FILE TOXCENTER
1372 FILE USPATFULL
3 FILE USPATOLD

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644 FILE USPAT2
10 FILE IPA
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(COLOR? OR COLOU?)
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COPPE? OR "CU" OR NICKE? OR "NI" OR CYSTEIN? OR "CYS" OR
"ANTI-OXIDANT")
L4 14 SEA L3(S)((MEDIA? OR MEDIUM?) (20A)(DEFINE?))
L5 14 DUP REM L4 (0 DUPLICATES REMOVED)
D IBIB ABS L5 1-14

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FILE STNINDEX

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 26 Nov 2020 (20201126/PD)

FILE LAST UPDATED: 26 Nov 2020 (20201126/ED)

HIGHEST GRANTED PATENT NUMBER: US10849261

HIGHEST APPLICATION PUBLICATION NUMBER: US20200375078

CA INDEXING IS CURRENT THROUGH 22 Nov 2020 (20201122/UPCA)

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FILE COVERS 1950 TO PATENT PUBLICATION DATE: 26 Nov 2020 (20201126/PD)

FILE LAST UPDATED: 27 Nov 2020 (20201127/ED)

HIGHEST GRANTED PATENT NUMBER: US10849261

HIGHEST APPLICATION PUBLICATION NUMBER: US20200375078

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 26 Nov 2020 (20201126/PD)

FILE LAST UPDATED: 26 Nov 2020 (20201126/ED)

HIGHEST GRANTED PATENT NUMBER: US10849261

HIGHEST APPLICATION PUBLICATION NUMBER: US20200375078

CA INDEXING IS CURRENT THROUGH 22 Nov 2020 (20201122/UPCA)

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FILE ADISCTI

FILE COVERS 1998 TO 27 Nov 2020 (20201127/ED)

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>>> FILE COVERS 1983 TO DATE <<<

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FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 25 November 2020 (20201125/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926
through 1968. These records have been re-indexed to match current
BIOSIS indexing.

FILE MEDLINE

FILE COVERS 1946 TO DATE.
FILE LAST UPDATED: 27 Nov 2020 (20201127/UP).

MEDLINE(R) is a registered trademark of the U.S. National Library of
Medicine (NLM).

The 2020 MeSH thesaurus is now available as a source of terminology
for your searches.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

See HELP RANGE before carrying out any RANGE search.

FILE SCISEARCH

FILE COVERS 1974 TO 23 Nov 2020 (20201123/ED)

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FILE BIOTECHNO
FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>
FILE COVERS 1980 TO 2003.
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FILE AGRICOLA
FILE LAST UPDATED: 10 NOV 2020 <20201110/UP>
FILE COVERS 1970 TO DATE

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INDEX (/BI), ABSTRACT (/AB), AND TITLE (/TI) FIELDS <<<

FILE CABA
FILE LAST UPDATED: 25 NOV 2020 <20201125/UP>
FILE COVERS 1973 TO DATE

<<< SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN
THE BASIC INDEX (/BI), ABSTRACT (/AB), AND TITLE (/TI) FIELDS >>>

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L5 ANSWER 1 OF 14 USPAT2 on STN
ACCESSION NUMBER: 2019:166288 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods
for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,

UNITED STATES
 Meier, Steven J., South San Francisco, CA, UNITED STATES
 STATES
 Varma, Sharat, South San Francisco, CA, UNITED STATES
 Yang, Yi, South San Francisco, CA, UNITED STATES
 Genentech, Inc., South San Francisco, CA, UNITED STATES
 (U.S. corporation)

PATENT ASSIGNEE(S):

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10829732	B2	20201110
APPLICATION INFO.:	US 2018-16151904		20181004 (16)
RELATED APPLN. INFO.:	Division of Ser. No. US 2015-14852311, filed on 11 Sep 2015, Pat. No. US 10131873 Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	22	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 11 Drawing Page(s)	
LINE COUNT:	4261	

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

SUMM . . . analog or precursor thereof, wherein the cell culture medium comprising the hypotaurine or an analog of precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell as compared to the color intensity of a composition comprising the polypeptide produced by the cell cultured in a cell culture medium that does not. . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by at least about 0.1% as compared to a . . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by about 5% to about 50% as compared to. . . embodiments herein, the hypotaurine or an analog or precursor thereof is selected from the group consisting of hypotaurine, s-carboxymethylcysteine, cysteamine, cysteinesulphinic acid, and taurine. In some of the embodiments herein, the cell culture medium comprising the hypotaurine or an analog or precursor thereof is a chemically defined cell culture medium. In some of the embodiments herein, the cell culture medium comprising the hypotaurine or an analog or precursor thereof is a chemically undefined cell culture medium. In some of the . . . In some of the embodiments herein, the cell is a mammalian cell. In some of the embodiments herein, the mammalian cell is a Chinese Hamster Ovary (CHO) cell. In some of the embodiments herein, the polypeptide is an antibody or fragment thereof.

SUMM . . . or precursor thereof, and wherein the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell as compared to the color intensity of a composition comprising the polypeptide produced by the cell cultured in a cell culture medium that does not. . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by at least about 0.1% as compared to a . . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by about 5% to about 50% as compared to. . . embodiments herein, the hypotaurine

or an analog or precursor thereof is selected from the group consisting of hypotaurine, s-carboxymethylcysteine, cysteamine, cysteinesulphinic acid, and taurine. In some of the embodiments herein, the cell culture medium is a chemically defined cell culture medium. In some of the embodiments herein, the cell culture medium is a chemically undefined cell culture medium. In some of the embodiments herein, the cell culture medium is a basal cell culture medium. In some of the . . . cell culture cycle. In some of the embodiments herein, the cell is a mammalian cell. In some embodiments, the mammalian cell is a Chinese Hamster Ovary (CHO) cell. In some of the embodiments herein, the polypeptide is an antibody. In some embodiments, the antibody is an IgG1 antibody. . . . is a liquid composition or a non-liquid composition. In some embodiments, the composition comprising the recovered polypeptide appears as a colorless or slightly colored liquid.

L5 ANSWER 2 OF 14 USPAT2 on STN

ACCESSION NUMBER: 2019:3991 USPAT2 Full-text
 TITLE: Cell culture compositions with antioxidants and methods for polypeptide production
 INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA, UNITED STATES
 Meier, Steven J., South San Francisco, CA, UNITED STATES
 Varma, Sharat, South San Francisco, CA, UNITED STATES
 Yang, Yi, South San Francisco, CA, UNITED STATES
 PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10676710	B2	20200609
APPLICATION INFO.:	US 2018-15997342		20180604 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14211416, filed on 14 Mar 2014, Pat. No. US 10017732		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	32	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)	
LINE COUNT:	4173	

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

SUMM . . . analog or precursor thereof, wherein the cell culture medium comprising the hypotaurine or an analog of precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell as compared to the color intensity of a composition comprising the polypeptide produced by the cell cultured in a cell culture medium that does not. . . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by at least about 0.1% as compared to a . . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by about 5% to about 50% as compared to. . . . embodiments herein, the hypotaurine or an analog or precursor thereof is selected from the group consisting of hypotaurine, s-carboxymethylcysteine, cysteamine, cysteinesulphinic acid, and taurine. In some of the embodiments herein, the cell culture medium comprising the hypotaurine or an analog or precursor thereof is a chemically defined cell culture medium. In some of the embodiments herein, the cell culture medium comprising the hypotaurine or an

analog or precursor thereof is a chemically undefined cell culture medium. In some of the. . . In some of the embodiments herein, the cell is a mammalian cell. In some of the embodiments herein, the mammalian cell is a Chinese Hamster Ovary (CHO) cell. In some of the embodiments herein, the polypeptide is an antibody or fragment thereof.

SUMM . . . or precursor thereof, and wherein the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell as compared to the color intensity of a composition comprising the polypeptide produced by the cell cultured in a cell culture medium that does not. . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by at least about 0.1% as compared to a. . . precursor thereof. In some embodiments, the cell culture medium comprising the hypotaurine or an analog or precursor thereof reduces the color intensity of a composition comprising the polypeptide produced by the cell by about 5% to about 50% as compared to. . . embodiments herein, the hypotaurine or an analog or precursor thereof is selected from the group consisting of hypotaurine, s-carboxymethylcysteine, cysteamine, cysteinesulphinic acid, and taurine. In some of the embodiments herein, the cell culture medium is a chemically defined cell culture medium. In some of the embodiments herein, the cell culture medium is a chemically undefined cell culture medium. In some of the embodiments herein, the cell culture medium is a basal cell culture medium. In some of the. . . cell culture cycle. In some of the embodiments herein, the cell is a mammalian cell. In some embodiments, the mammalian cell is a Chinese Hamster Ovary (CHO) cell. In some of the embodiments herein, the polypeptide is an antibody. In some embodiments, the antibody is an IgG1 antibody.. . . is a liquid composition or a non-liquid composition. In some embodiments, the composition comprising the recovered polypeptide appears as a colorless or slightly colored liquid.

L5 ANSWER 12 OF 14 SCISEARCH COPYRIGHT (c) 2020 Clarivate Analytics on STN

ACCESSION NUMBER: 2015:271312 SCISEARCH Full-text

THE GENUINE ARTICLE: AZ8HD

TITLE: Iron mediated tryptophan oxidation and vitamin B12 carryover caused a brown color formation of protein drug substance manufactured in CHO cells using chemically defined media

AUTHOR: Xu, Jianlin (Reprint); Jin, Mi; Song, Hangtian; Huang, Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger, Kirby; Tao, Li; Li, Zheng Jian

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CORPORATE SOURCE: Bristol Myers Squibb Co, Pharmaceut Dev, New York, NY 10154 USA

COUNTRY OF AUTHOR: USA

SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (16 MAR 2014) Vol. 247. MA 385-BIOT.
ISSN: 0065-7727.

PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.

DOCUMENT TYPE: Conference; Journal

LANGUAGE: English

REFERENCE COUNT: 0

ENTRY DATE: Entered STN: 23 Feb 2015

Last Updated on STN: 23 Feb 2015

TI Iron mediated tryptophan oxidation and vitamin B12 carryover caused a brown color formation of protein drug substance manufactured in CHO cells using chemically defined media

WEST Search History

DATE: Friday, November 27, 2020

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☐	L6	L5 and (iron\$4 or ferrou\$4 or ferric\$4 or zinc\$4 or "zn" or coppe\$4 or "cu" or nicke\$4 or "ni" or cystein\$4 or "cys" or "anti-oxidant")	95
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☐	L1	("cho" or (chines\$4 adj3 ham\$4 adj3 ovar\$4)) same (color\$3 or colou\$4)	2366

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BIB DATA SHEET

CONFIRMATION NO. 3885

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/996,030	08/18/2020	435	1652	070816-02250

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DR
 11/22/2020

**** CONTINUING DATA *******
 This appln claims benefit of 63/065,012 08/13/2020

**** FOREIGN APPLICATIONS *******

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
 09/17/2020

Foreign Priority claimed 35 USC 119(a-d) conditions met Verified and Acknowledged	☐ Yes ☒ No ☐ Yes ☒ No <u>/DELIA M RAMIREZ/</u> Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY NY	SHEETS DRAWINGS 60	TOTAL CLAIMS 30	INDEPENDENT CLAIMS 3
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 UNITED STATES

TITLE
 ANTI-VEGF PROTEIN COMPOSITIONS AND METHODS FOR PRODUCING THE SAME

FILING FEE RECEIVED 4080	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
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27 NOV 2020
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644 FILE USPAT2
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"ANTI-OXIDANT")
L4 14 SEA L3(S)((MEDIA? OR MEDIUM?) (20A)(DEFINE?))
L5 14 DUP REM L4 (0 DUPLICATES REMOVED)
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CIELAB color space

The **CIELAB color space** (also known as **CIE $L^*a^*b^*$** or sometimes informally abbreviated as "Lab") is a color space defined by the International Commission on Illumination (abbreviated CIE) in 1976. It expresses color as three values: L^* for the lightness from black (0) to white (100), a^* from green (−) to red (+), and b^* from blue (−) to yellow (+). CIELAB was designed so that the same amount of numerical change in these values corresponds to roughly the same amount of visually perceived change.

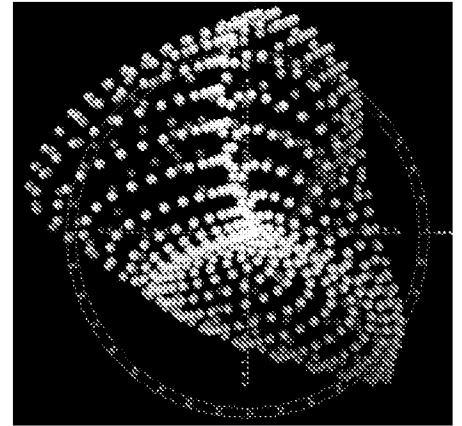
With respect to a given white point, the CIELAB model is device-independent—it defines colors independently of how they are created or displayed. The CIELAB color space is typically used when graphics for print have to be converted from RGB to CMYK, as the CIELAB gamut includes both the gamuts of the RGB and CMYK color models.

Because three parameters are measured, the space itself is a three-dimensional real number space, which allows for infinitely many possible colors. In practice, the space is usually mapped onto a three-dimensional integer space for digital representation, and thus the L^* , a^* , and b^* values are usually absolute, with a pre-defined range. The lightness value, L^* , represents the darkest black at $L^* = 0$, and the brightest white at $L^* = 100$. The color channels, a^* and b^* , represent true neutral gray values at $a^* = 0$ and $b^* = 0$. The a^* axis represents the green–red component, with green in the negative direction and red in the positive direction. The b^* axis represents the blue–yellow component, with blue in the negative direction and yellow in the positive direction. The scaling and limits of the a^* and b^* axes will depend on the specific implementation, as described below, but they often run in the range of ± 100 or -128 to $+127$ (signed 8-bit integer).

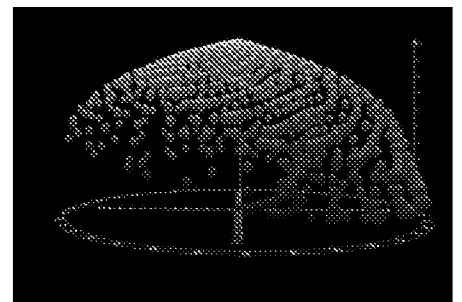
The CIELAB color space was derived from the prior "master" CIE 1931 XYZ color space, which predicts which spectral power distributions will be perceived as the same color (see metamerism), but is not particularly perceptually uniform.^[1] Strongly influenced by the Munsell color system, the intention behind CIELAB was to create a space that can be computed via simple formulas from the CIE XYZ space but is more perceptually uniform than CIE XYZ.^[2] When storing color values using limited precision, using a perceptually uniform color space can improve the reproduction of tones.

CIELAB colors are defined relative to the white point of the CIE XYZ space from which they were converted; thus CIELAB values do not define absolute colors unless the white point is also specified. Often, in practice, the white point is assumed to follow a standard and is not explicitly stated (e.g., for "absolute colorimetric" rendering intent, the International Color Consortium $L^*a^*b^*$ values are relative to CIE standard illuminant D50, while they are relative to the unprinted substrate for other rendering intents).^[3]

The lightness correlate in CIELAB is calculated using the cube root of the relative luminance.



CIELAB color space top view



CIELAB color space front view

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- From CIELAB to CIEXYZ

Hunter Lab

- Approximate formulas for K_a and K_b
- As an Adams chromatic valence space

Cylindrical model

See also

References

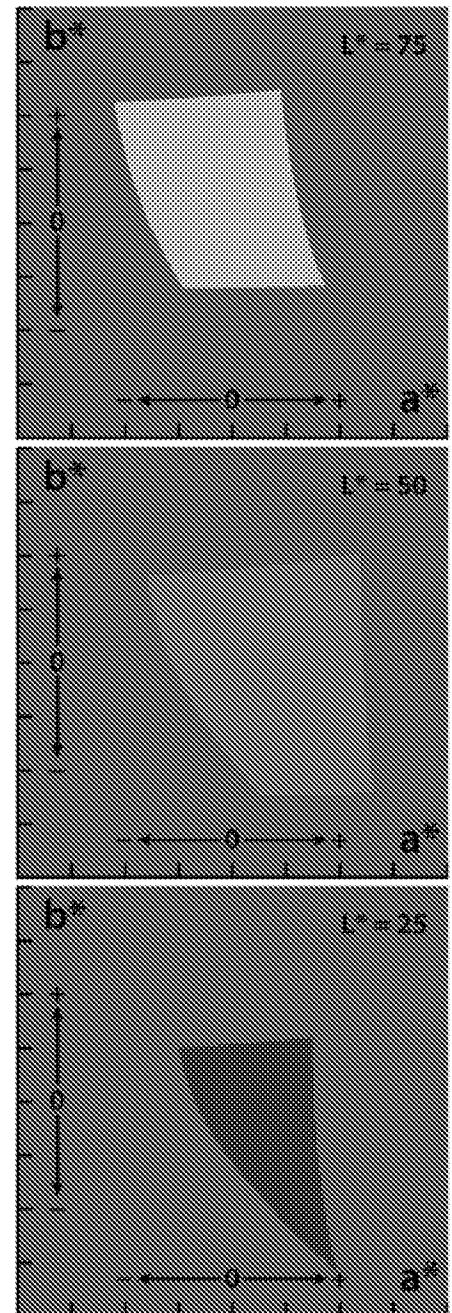
External links

Advantages

Unlike the **RGB** and **CMYK** color models, *CIELAB* is designed to approximate human vision. It aspires to perceptual uniformity, and its *L* component closely matches human perception of lightness (although it does not take the **Helmholtz–Kohlrausch effect** into account). Thus, it can be used to make accurate color balance corrections by modifying output curves in the a^* and b^* components, or to adjust the lightness contrast using the L^* component. In RGB or CMYK spaces, which model the output of physical devices rather than human visual perception, these transformations can be done only with the help of appropriate blend modes in the editing application.

Because the *CIELAB* space is larger than the gamut of computer displays and printers and because the visual stepwidths are relatively indifferent to the color area, a bitmap image represented in CIELAB requires more data per pixel to obtain the same precision as an RGB or CMYK bitmap. In the 1990s, when computer hardware and software were limited to storing and manipulating mostly 8-bit/channel bitmaps, converting an RGB image to Lab and back was a very lossy operation. With 16-bit/channel and floating-point support now common, the loss due to quantization is negligible.

CIELAB is copyright- and licence-free. As it is fully defined mathematically, the CIELAB model is public domain. It is in all respects freely usable and integrable (as are systematic CIELAB / HLC color value tables).



The CIE 1976 (L^* , a^* , b^*) color space (CIELAB), showing only colors that fit within the sRGB gamut (and can therefore be displayed on a typical computer display). Each axis of each square ranges from ~ 128 to 127.

A large portion of the CIELAB coordinate space cannot be generated by spectral distributions. These coordinates therefore fall outside of human vision and are not truly "colors".

Where CIELAB is used

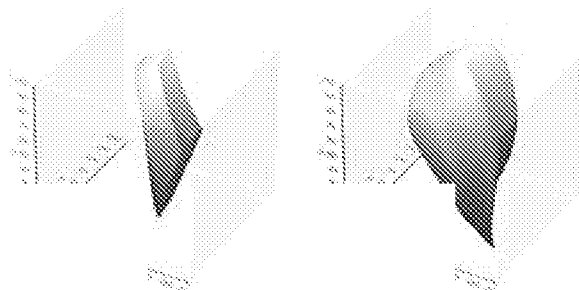
Some systems and software applications that support CIELAB include:

- CIELAB D50 is available in Adobe Photoshop, where it is called "Lab mode".^{[4][5]}
- CIELAB is available in Affinity Photo by changing the document's Colour Format to "Lab (16 bit)".
- CIELAB D50 is available in ICC profiles as a profile connection space named "Lab color space".^[3]
- CIELAB is a supported color space in TIFF image files.^[6]
- CIELAB is available in PDF documents, where it is called the "Lab color space".^{[7][8]}
- CIELAB is an option in Digital Color Meter on macOS described as "L*a*b*".
- CIELAB is available in the RawTherapee photo editor, where it is called the "Lab color space".^[9]



An example of color enhancement using LAB color mode in Photoshop. The left side of the photo is enhanced, while the right side is normal.

CIELAB coordinates



The sRGB gamut (*left*) and visible gamut under D65 illumination (*right*) plotted within the CIELAB color space. *a* and *b* are the horizontal axes; *L* is the vertical axis.

The three coordinates of CIELAB represent the lightness of the color ($L^* = 0$ yields black and $L^* = 100$ indicates diffuse white; specular white may be higher), its position between red and green (a^* , where negative values indicate green and positive values indicate red) and its position between yellow and blue (b^* , where negative values indicate blue and positive values indicate yellow). The asterisks (*) after L , a and b are pronounced *star* and are part of the full name, since they represent L^* , a^* and b^* , to distinguish them from Hunter's L , a , and b , described below.

Since the $L^*a^*b^*$ model has three coordinates, it can be represented properly only in a three-dimensional space.^[10] Two-dimensional depictions include chromaticity diagrams: sections of the color solid with a fixed lightness. It is crucial to realize that the visual representations of the full gamut of colors in this model are never accurate; they are there just to help in understanding the concept.

Because the red-green and yellow-blue opponent channels are computed as differences of lightness transformations of (putative) cone responses, CIELAB is a chromatic value color space.

A related color space, the CIE 1976 (L^* , u^* , v^*) color space (a.k.a. CIELUV), preserves the same L^* as $L^*a^*b^*$ but has a different representation of the chromaticity components. CIELAB and CIELUV can also be expressed in cylindrical form (CIELCH^[11] and CIELCH_{uv}, respectively), with the chromaticity components replaced by correlates of chroma and hue.

Since the work on CIELAB and CIELUV, the CIE has been incorporating an increasing number of color appearance phenomena into their models, to better model color vision. These color appearance models, of which CIELAB is a simple example,^[12] culminated with CIECAM02.

Perceptual differences

The nonlinear relations for L^* , a^* , and b^* are intended to mimic the nonlinear response of the eye. Furthermore, uniform changes of components in the $L^*a^*b^*$ color space aim to correspond to uniform changes in perceived color, so the relative perceptual differences between any two colors in $L^*a^*b^*$ can be approximated by treating each color as a point in a three-dimensional space (with three components: L^* , a^* , b^*) and taking the Euclidean distance between them.^[13]

RGB and CMYK conversions

There are no formulas for conversion between RGB or CMYK values and $L^*a^*b^*$, because the RGB and CMYK color models are device-dependent. The RGB or CMYK values first must be transformed to a specific absolute color space, such as sRGB or Adobe RGB. This adjustment will be device-dependent, but the resulting data from the transform will be device-independent, allowing data to be transformed to the CIE 1931 color space and then transformed into $L^*a^*b^*$.

Range of coordinates

As mentioned previously, the L^* coordinate ranges from 0 to 100. The possible range of a^* and b^* coordinates is independent of the color space that one is converting from, since the conversion below uses X and Z, which come from RGB.

Converting between CIELAB and CIEXYZ coordinates

From CIEXYZ to CIELAB

$$\begin{aligned} L^* &= 116 f\left(\frac{Y}{Y_n}\right) - 16 \\ a^* &= 500 \left(f\left(\frac{X}{X_n}\right) - f\left(\frac{Y}{Y_n}\right) \right) \\ b^* &= 200 \left(f\left(\frac{Y}{Y_n}\right) - f\left(\frac{Z}{Z_n}\right) \right) \end{aligned}$$

where, being $t=Y/Y_n$:

$$f(t) = \begin{cases} \sqrt[3]{t} & \text{if } t > \delta^3 \\ \frac{t}{3\delta^2} + \frac{4}{29} & \text{otherwise} \end{cases}$$

$$\delta = \frac{6}{29}$$

Here, X_n , Y_n and Z_n are the CIE XYZ tristimulus values of the reference white point (the subscript n suggests "normalized").

Under Illuminant D65 with normalization $Y = 100$, the values are

$$\begin{aligned} X_n &= 95.0489, \\ Y_n &= 100, \\ Z_n &= 108.8840 \end{aligned}$$

Values for illuminant D50 are

$$\begin{aligned} X_n &= 96.4212, \\ Y_n &= 100, \\ Z_n &= 82.5188 \end{aligned}$$

The division of the domain of the f function into two parts was done to prevent an infinite slope at $t = 0$. The function f was assumed to be linear below some $t = t_0$, and was assumed to match the $t^{1/3}$ part of the function at t_0 in both value and slope. In other words:

$$\begin{aligned} t_0^{1/3} &= mt_0 + c && \text{(match in value)} \\ \frac{1}{3}t_0^{-2/3} &= m && \text{(match in slope)} \end{aligned}$$

The intercept $f(0) = c$ was chosen so that L^* would be 0 for $Y = 0$: $c = 16/116 = 4/29$. The above two equations can be solved for m and t_0 :

$$\begin{aligned} m &= \frac{1}{3}\delta^{-2} && = 7.787037\dots \\ t_0 &= \delta^3 && = 0.008856\dots \end{aligned}$$

where $\delta = 6/29$.^[14]

From CIELAB to CIEXYZ

The reverse transformation is most easily expressed using the inverse of the function f above:

$$\begin{aligned}
 X &= X_n f^{-1} \left(\frac{L^* + 16}{116} + \frac{a^*}{500} \right) \\
 Y &= Y_n f^{-1} \left(\frac{L^* + 16}{116} \right) \\
 Z &= Z_n f^{-1} \left(\frac{L^* + 16}{116} - \frac{b^*}{200} \right)
 \end{aligned}$$

where

$$f^{-1}(t) = \begin{cases} t^3 & \text{if } t > \delta \\ 3\delta^2 \left(t - \frac{4}{29} \right) & \text{otherwise} \end{cases}$$

and where $\delta = 6/29$.

Hunter Lab

The Hunter Lab color space, defined in 1948^{[15][16]} by Richard S. Hunter, is another color space sometimes referred to as "Lab". Like CIELAB, it was also designed to be computed via simple formulas from the CIEXYZ space, but to be more perceptually uniform than CIEXYZ. Hunter named his coordinates L , a , and b ; the CIELAB space, defined years later in 1976, named its coordinates L^* , a^* , and b^* to distinguish them from Hunter's coordinates.

L is a correlate of lightness, and is computed from the Y tristimulus value using Priest's approximation to Munsell value:

$$L = 100 \sqrt{Y/Y_n}$$

where Y_n is the Y tristimulus value of a specified white object. For surface-color applications, the specified white object is usually (though not always) a hypothetical material with unit reflectance that follows Lambert's law. The resulting L will be scaled between 0 (black) and 100 (white); roughly ten times the Munsell value. Note that a medium lightness of 50 is produced by a luminance of 25, since $100 \sqrt{25/100} = 100 \cdot 1/2$

a and b are termed opponent color axes. a represents, roughly, Redness (positive) versus Greenness (negative). It is computed as:

$$a = K_a \left(\frac{X/X_n - Y/Y_n}{\sqrt{Y/Y_n}} \right)$$

where K_a is a coefficient that depends upon the illuminant (for D65, K_a is 172.30; see approximate formula below) and X_n is the X tristimulus value of the specified white object.

The other opponent color axis, b , is positive for yellow colors and negative for blue colors. It is computed as:

$$b = K_b \left(\frac{Y/Y_n - Z/Z_n}{\sqrt{Y/Y_n}} \right)$$

where K_b is a coefficient that depends upon the illuminant (for D65, K_b is 67.20; see approximate formula below) and Z_n is the Z tristimulus value of the specified white object.^[17]

Both a and b will be zero for objects that have the same chromaticity coordinates as the specified white objects (i.e., achromatic, grey, objects).

Approximate formulas for K_a and K_b

In the previous version of the Hunter *Lab* color space, K_a was 175 and K_b was 70. Hunter Associates Lab discovered that better agreement could be obtained with other color difference metrics, such as CIELAB (see above) by allowing these coefficients to depend upon the illuminants. Approximate formulae are:

$$K_a \approx \frac{175}{198.04} (X_n + Y_n)$$

$$K_b \approx \frac{70}{218.11} (Y_n + Z_n)$$

which result in the original values for Illuminant C, the original illuminant with which the *Lab* color space was used.

As an Adams chromatic valence space

Adams chromatic valence color spaces are based on two elements: a (relatively) uniform lightness scale, and a (relatively) uniform chromaticity scale.^[18] If we take as the uniform lightness scale Priest's approximation to the Munsell Value scale, which would be written in modern notation as:

$$L = 100 \sqrt{Y/Y_n}$$

and, as the uniform chromaticity coordinates:

$$c_a = \frac{X/X_n}{Y/Y_n} - 1 = \frac{X/X_n - Y/Y_n}{Y/Y_n}$$

$$c_b = k_e \left(1 - \frac{Z/Z_n}{Y/Y_n} \right) = k_e \frac{Y/Y_n - Z/Z_n}{Y/Y_n}$$

where k_e is a tuning coefficient, we obtain the two chromatic axes:

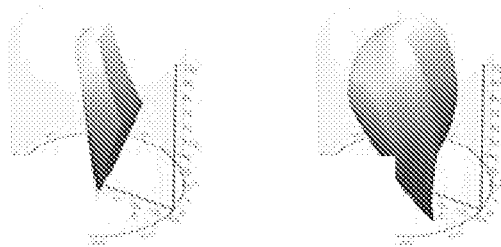
$$a = K \cdot L \cdot c_a = K \cdot 100 \frac{X/X_n - Y/Y_n}{\sqrt{Y/Y_n}}$$

and

$$b = K \cdot L \cdot c_b = K \cdot 100k_e \frac{Y/Y_n - Z/Z_n}{\sqrt{Y/Y_n}}$$

which is identical to the Hunter *Lab* formulas given above if we select $K = K_a/100$ and $k_e = K_b/K_a$. Therefore, the Hunter Lab color space is an Adams chromatic valence color space.

Cylindrical model



The sRGB gamut (*left*) and visible gamut under D65 illumination (*right*) plotted within the CIELCh color space. L is the vertical axis; C is the cylinder radius; h is the angle around the circumference.

The "CIELCh" or "CIEHLC" space is a color space based on CIELAB, which uses the polar coordinates C^* (chroma, relative saturation) and h° (hue angle, angle of the hue in the CIELab color wheel) instead of the Cartesian coordinates a^* and b^* . The CIELab lightness L^* remains unchanged.

The conversion of a^* and b^* to C^* and h° is performed as follows:

$$C^* = \sqrt{a^{*2} + b^{*2}}, \quad h^\circ = \text{atan2}(b^*, a^*)$$

Conversely, given the polar coordinates, conversion to Cartesian coordinates is achieved with:

$$a^* = C^* \cos(h^\circ), \quad b^* = C^* \sin(h^\circ)$$

The LCh color space is not the same as the HSV, HSL or HSB color models, although their values can also be interpreted as a base color, saturation and lightness of a color. The HSL values are a polar coordinate transformation of what is technically defined RGB cube color space. LCh is still perceptually uniform.

Further, H and h are not identical, because HSL space uses as primary colors the three additive primary colors red, green, and blue ($H = 0, 120, 240^\circ$). Instead, the LCh system uses the four colors red, yellow, green, and blue ($h = 0, 90, 180, 270^\circ$). Regardless the angle h , $C = 0$ means the achromatic colors, that is, the gray axis.

The simplified spellings LCh, LCH and HLC are common, but the latter presents a different order. HCL color space (Hue-Chroma-Luminance) on the other hand is a commonly used alternative name for the $L^*C^*h(uv)$ color space, also known as the *cylindrical representation* or *polar CIELUV*. This name is commonly used by information visualization practitioners who want to present data without the bias implicit in using varying saturation.^{[19][20]}

See also

- [Color theory](#)
- [Opponent color theory](#)
- [HSL and HSV](#)
- [RGB color model](#)
- [CMYK color model](#)
- [CIECAM02](#)
- [HCL color space](#)

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External links

- Demonstrative color conversion applet (http://www.cs.rit.edu/~ncs/color/a_spaces.html)
- CIELAB Color Space (<http://docs-hoffmann.de/cielab03022003.pdf>) by Gernot Hoffmann, includes explanations of L*a*b* conversion formulae, graphical depictions of various gamuts plotted in L*a*b* space, and PostScript code for performing the color transformations.
- Whitepaper on understanding colors (https://www.xrite.com/-/media/xrite/files/whitepaper_pdfs/l10-001_a_guide_to_understanding_color_communication/l10-001_understand_color_en.pdf) by X-rite.

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This page was last edited on 11 November 2020, at 01:30 (UTC).

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	Filing Date		2020-08-17
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	Examiner Name	Delia M. Ramirez	
	Attorney Docket Number	070816-02250	

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11/28/2020

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/D.R/	75	10406226	B2	2019-09-10	Regeneron Pharmaceuticals, Inc.	
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/DELIA M RAMIREZ/

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		16996030
Filing Date		2020-08-17
First Named Inventor	Shawn Lawrence	
Art Unit		1652
Examiner Name	Delia M. Ramirez	
Attorney Docket Number		070816-02250

Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
/D.R./	1	20200246423	A1	2020-08-06	Coherus BioSciences Inc.	
↓	2	20080009040	A1	2008-01-10	Baxter Healthcare Corporation	
↓	3	20070212770	A1	2007-09-13	Baxter Healthcare Corporation	
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↓	5	20170174779	A1	2017-06-22	Regeneron Pharmaceuticals, Inc.	
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/D.R/	11	20190388539	A1	2019-12-26	Regeneron Pharmaceuticals, Inc.	
↓	12	20140314779	A1	2014-10-23	Genentech, Inc.	
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/D.R/	1	WO2020/160133	WO	A1	2020-08-06	Amgen Inc.		☐
↓	2	WO2007/077217	WO	A2	2007-07-12	Baxter International Inc.		☐
	3	WO2001/092337	WO	A2	2001-12-06	Bristol-Myers Squibb Company		☐
↓	4	WO2005/000895	WO	A2	2005-01-06	Regeneron Pharmaceuticals, Inc.		☐

/DELIA M RAMIREZ/

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/D.R./	5	EP1458861	EP	B1	2015-04-11		WO2003/051914	☐
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EXAMINER SIGNATURE

Examiner Signature	/DELIA M RAMIREZ/	Date Considered	11/28/2020
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<i>Notice of References Cited</i>	Application/Control No. 16/996,030		Applicant(s)/Patent Under Reexamination Lawrence et al.	
	Examiner DELIA M RAMIREZ		Art Unit 1652	Page 1 of 1

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*	B	US-7396664-B2	07-2008	Daly; Thomas J.	C07K14/71	424/134.1
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/996,030	08/18/2020	Shawn Lawrence	070816-02250	3885
151431	7590	03/24/2021	EXAMINER	
Kramer Levin Naftalis & Frankel LLP			RAMIREZ, DELIA M	
1177 Avenue of the Americas			ART UNIT	PAPER NUMBER
New York, NY 10036			1652	
			NOTIFICATION DATE	DELIVERY MODE
			03/24/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

dtorniali@kramerlevin.com
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DETAILED ACTION

Status of the Application

Claims 1-30 are pending.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's amendment of claims 1-2, 9, 17-19, 22-24, 26-27, 30, and amendments to the specification and title as submitted in a communication filed on 3/2/2021 are acknowledged.

Claims 1-8, 10-13, 15-16, 23-30 and claims 9, 14, 17, 18-22 in part are at issue and are being examined herein.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The previous objection to the title of the invention is hereby *withdrawn* by virtue of Applicant's amendment.
2. The previous objection to the specification due to the presence of an embedded hyperlink and/or other form of browser-executable code is hereby *withdrawn* by virtue of Applicant's amendment.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 12/15/2020, 2/12/2021 and 2/19/2021 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

4. Claim 27 is objected to due to the recitation of “wherein one or more concentration of (i) to (vi) are not maintained”. To enhance clarity and to be grammatically correct, the term should be amended to recite “wherein one or more of the concentrations of (i) to (vi) are not maintained”. Appropriate correction is required.

Claim Rejections - 35 USC § 112(b) or Second Paragraph (pre-AIA)

5. Claims 1-30 remain rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. New grounds of rejection are necessitated by amendment.

6. Claim 1 (claims 2-17 dependent thereon) is indefinite in the recitation of “... aflibercept composition having a target value of aflibercept variants.....comprising: (a) providing.....; (b) culturing said.....; (c) clarifying and harvesting the aflibercept sample produced by said host cell, wherein the target value of aflibercept variants is obtained by using....” for the following reasons. It is unclear if the method requires all of steps (a), (b) and (c) or one of steps (a), (b) or (c) because there is no “and” between steps (b) and (c). It is also unclear as to what a “target value of aflibercept variants” is within the context of the claim. Does the term “value” refer to a certain amount of aflibercept variants (e.g., concentration/amount of variants X, Y and Z)? Does the term “value” refer to a certain number of types of aflibercept variants (e.g., 2 different types of variants, 3 different types of variants, 4 different types of variants etc..)? Applicant argues that the specification explains that a target value of variants is obtained by preparation of aflibercept using suitable conditions that result in a reduction in protein variants of aflibercept. Applicant states that the claims set forth the conditions to prepare aflibercept and to obtain aflibercept with the desired amount of aflibercept variants. This is not found persuasive. The Examiner acknowledges that the claim recites conditions (concentrations) for obtaining the variants. However, for

the reasons extensively discussed above and below, the term “target value of aflibercept variants” is indefinite and the conditions recited in the claim do not define the unclear terminology.

Moreover, as written, it is unclear as to what is the intended meaning of the term “clarifying” as it relates to the aflibercept sample. Does the term refer to purifying? Does the term refer to making the sample more translucent? If the intended limitation is purifying, the claim should be amended accordingly. In addition, the terms “aflibercept” and “aflibercept variants” remain unclear because one cannot determine from the specification if the term “aflibercept” as used in the claims is associated to a single amino acid sequence or not. In the absence of a sequence identifier associated with the term “aflibercept”, it is unclear as to what constitutes a variant of “aflibercept”, particularly if the term “aflibercept” intends to encompass a genus of proteins and not a single one. For example, if the term “aflibercept” is intended to encompass more than a single protein, a protein comprising SEQ ID NO: X as well as a protein comprising SEQ ID NO: X minus the last 3 amino acids of the C-terminus can be considered to be “aflibercept”. If the term is intended to encompass a single protein, the protein comprising all of SEQ ID NO: X minus the last 3 amino acids of the C-terminus would be considered an “aflibercept variant”.

Applicant argues that the aflibercept is an exemplary VEGF receptor-based chimeric molecule referred to as VEGFR1R2-FcΔC1(a), also known as EYLEA ® and that in certain exemplary embodiments, aflibercept comprises SEQ ID NO: 55. Applicant further argues that the specification states that protein variants in the case of aflibercept can comprise, but are not limited to, oxidation variants which can result from oxidation, and deamidation. Therefore, Applicant is of the opinion that the specification provides guidance as to what the terms “aflibercept” and “aflibercept variants” constitute.

Applicant’s arguments have been fully considered but not deemed persuasive to conclude that the terms “aflibercept” and “aflibercept variants” are definite in view of the teachings of the specification. The Examiner acknowledges the teachings of the specification. However, it is noted that, as pointed out by Applicant in the response to the prior Office action, the specification discloses that VEGFR1R2-FcΔC1(a) and the polypeptide of SEQ ID NO: 55 are merely *exemplary species of what is encompassed*

by the term “aflibercept”. Similarly, the specification discloses that aflibercept variants *can comprise but are not limited to* oxidation or deamination variants. As such, it is abundantly clear from the specification that aflibercept variants that result from oxidation and/or deamination of amino acids are simply examples of what is encompassed by the term “aflibercept variants”. Therefore, contrary to Applicant’s assertions, the specification merely provide examples of what these terms can represent and does not provide a definition of the terms so that one of skill in the art can determine the metes and bounds of the terms “aflibercept” and “aflibercept variants”. Correction is required.

7. Claims 1-8, 19, 21, 23, 25 (claims 9-17, 20, 22, 24, 26-30 dependent thereon) remain indefinite in the recitation of “less than or equal to about X”, “no more than about”, and “less than about”, for the reasons of record. Applicant submits that in the context of the specification and the claims, one of skill in the art would understand that “about” accommodates minor variations including variations in measurements. This is not found persuasive. The Examiner agrees that the term “about” by itself is not indefinite. However, as explained in the prior Office action, *the issue in the instant case is the combination of “about” with additional language that in combination render the claims indefinite*. As explained in the prior Office action, the term “about” encompasses *a range* which includes values which are higher and lower than the recited reference value. The term “less than” implies that only values less than the recited reference value are encompassed. The term “no more than” implies that only values equal or less to the reference value are encompassed. Therefore, in the absence of a clear definition of what is encompassed by the term “about”, the terms “less than about”, “less than or equal to about X” and “no more than about” are unclear and confusing since the terms refer to values which are (a) less, or (b) less or equal than undefined values which are either higher or lower than the recited reference values. In essence, the terms eliminate the relevance of the recited reference points because the reference values becomes variable and undefined. Correction is required.

8. Claim 2 is indefinite in the recitation of “target value of aflibercept variants” for the following reasons. It is unclear as to what a “target value of aflibercept variants” is within the context of the claim. Does the term “value” refer to a certain amount of aflibercept variants (e.g., concentration/amount of

variants X, Y and Z)? Does the term “value” refer to a certain number of types of aflibercept variants (e.g., 2 different types of variants, 3 different types of variants, 4 different types of variants etc..)? In addition, the terms “aflibercept” and “aflibercept variants” remain unclear because one cannot determine from the specification if the term “aflibercept” as used in the claims is associated to a single amino acid sequence or not. In the absence of a sequence identifier associated with the term “aflibercept”, it is unclear as to what constitutes a variant of “aflibercept”, particularly if the term “aflibercept” intends to encompass a genus of proteins and not a single one. See extensive discussion above with regard to the indefiniteness of these terms as it relate to claim 1. Correction is required.

9. Claim 10 remains indefinite in the recitation of “wherein said clarified harvest comprises one or more...” because there is no antecedent basis for “the” clarified harvest in claim 1 or 10. Applicant argues that the amendment made to claim 1 addresses this issue. However, it is noted that claim 1 as amended recites “clarifying and harvesting the aflibercept sample”. There is no recitation of a “harvest” in claim 1. If the intended term is “wherein the aflibercept sample of step (c)”, the claim should be amended accordingly. Correction is required.

10. Claims 16 and 18 (claims 17, 19-22 dependent thereon) remain indefinite in the recitation of “wherein said color is characterized in the CIE L*, a*, B* color space where L* is about 70 to about 99...” and “wherein, in the CIEL*, a*, b* color space is about...” for the reasons of record. Applicant argues that the claims recite a white point because there is a requirement for L* to be about 70 to about 99, thus defining a white point. Applicant asserts that L* represents the degree of lightness of a color on a scale of 0-100 with 0 being the darkest and 100 the lightest so that a value of 0 for L* is black and a value of 100 for L* is white. This is not found persuasive. The L* parameter is part of the three parameters that are required to define a CIELAB color. Therefore, the value ranges recited in the claims for L*, a* and b* merely define a CIELAB color. However, as previously noted, *a CIELAB color is not an absolute color*. It is reiterated herein and also specifically stated in the Wikipedia article previously provided, “CIELAB colors are defined relative to the white point of the CIEXYZ space from which they are converted; thus CIELAB values do not define absolute colors unless the white point is also specified”

(emphasis added). Therefore, in the absence of a value for a white point, claims 16 and 18 refer to a relative color. For examination purposes, no patentable weight will be given to the terms. Claim 16 will be interpreted as a duplicate of claim 1. Correction is required.

11. Claims 16, 17, 18, 24, 26 (claims 19-22 dependent thereon) remain indefinite in the recitation of “concentration of aflibercept is normalized to 5.0 g/l”, and “wherein the concentration of protein ... is normalized to 5.0 g/L” for the reasons of record. Applicant argues that one of skill in the art would understand that the normalization refers to the concentration of a protein for purposes of making the color measurement and the ability to compare one situation to a next situation. Applicant argues that normalization accounts for any difference in measurement resulting solely by concentration of a protein in a given sample. Applicant asserts that color assessment between multiple samples was normalized against protein concentration in order to assure a meaningful assessment/comparison. This is not found persuasive. The Examiner fully agrees that a meaningful comparison of color requires normalization of protein concentration so that color determination is made at the same concentration of the recited protein. However, the issue in the instant case is the lack of clarity of the term “concentration of aflibercept is normalized to 5.0 g/L” as used in the claims. If the requirement is to have a particular color at a concentration of aflibercept of 5 g/L, then it is unclear as to how the term “normalized ” further limits the claims. If claim 16 were to recite “wherein said aflibercept sample has a yellow-brown color....when the concentration of aflibercept is 5 g/L”, it would be clear to one of skill in the art that the required color has to be present when the concentration of aflibercept of 5 g/L. In other words, the “normalization” is already present in the requirement of an aflibercept concentration of 5 g/L. It appears from the specification that Applicant has used the protein concentration of 5 g/L as the protein concentration required to make a color measurement/color determination. Therefore, if the intended limitation is the presence of a particular color in an aflibercept sample, wherein the color is determined at a concentration of aflibercept of 5 g/L, the claims be amended to delete the term “normalized to”. Correction is required.

12. Claim 17 is indefinite in the recitation of “...method of claim 16, wherein said yellow-brown of (b) color is.....clarified harvest....” for the following reasons. First, there is no antecedent basis in claim

1 for the “clarified” harvest. Applicant argues that the amendments made to claim 17 address this issue. However, it is noted that claim 1 as amended recites “clarifying and harvesting the aflibercept sample”. There is no recitation of a “harvest” in claim 1. Furthermore, it is unclear as to what is the intended meaning of “yellow brown of (b) color”. There is no antecedent basis for “(b)” in claim 16, or antecedent basis for “yellow brown” in claim 1. For examination purposes, claim 17 will be interpreted as a duplicate of claim 1 as interpreted above. Correction is required.

13. Claims 17-18 (claims (claims 19-22 dependent thereon) were indefinite in the recitation of “European Color Standard BY_x” for the reasons of record. As explained in the prior Office action, while the prior art discloses European Pharmacopeia color standards, it was unclear if the recited European standards are the same as the European Pharmacopeia color standards. In view of Applicant’s assertions as set forth on page 13 of the response of 3/2/2021 asserting that the European Color Standards recited in the claims are the same as the European Pharmacopeia color standards, this rejection is hereby *withdrawn*.

14. Claim 18 (claims 19-22 dependent thereon) is indefinite in the recitation of “wherein the color of said harvest is characterized as follows: a. no more.....e. BY₃; f. between European color....; and/or wherein, in the CIE L*, a*, b*.....” for the following reasons. The term “and/or” after item f. implies that one could have a combination of all the colors of items a.-f and the CIELAB color having the recited parameters due to the recitation of “and”, which is unclear and confusing because one cannot have, for example, a color that is between colors BY₂ and BY₃, and at the same time a color BY₅. If the intended limitation is “wherein said color of said harvest is: a. no more yellow-brown than...BY₂.....e. between ...BY₂ and BY₃; f. between...BY₂ and BY₄; or g. a color in the CIE L*...color space wherein L* is.....”, the claim be amended accordingly. No patentable weight will be given to limitations regarding color. Correction is required.

15. Claim 22 is indefinite in the recitation of “wherein decreasing said metal concentration in said CDM by one half reduced color of said clarified harvest with an increase in a titer of said host cells in said CDM compared to aflibercept produced by said host cells cultured in said CDM where said metal

concentration is not decreased” for the following reasons. First, it is unclear if the term “said metal concentration” refers to (a) all of the iron, copper, nickel, and zinc concentrations recited in parts i.-iv. of claim 19, (b) the concentration of at least one of i.-vi., or (c) the concentration of any metal that could be in the CDM that is not iron, copper, nickel, or zinc. Second, there is no antecedent basis for the clarified harvest. Third, the term “clarified” is unclear because one cannot determine if the term refers to a “purified” harvest or if the term refers to a harvest that is translucent. Fourth, the claim does not require a comparison with the corresponding harvest obtained from an identical method wherein the metal concentration is reduced. Instead, the claim requires comparison with any aflibercept composition obtained at any step of the downstream processing of the cells/culture medium. As such, the comparison can be made with the extracellular medium that comprises aflibercept before any purification step, the elution of the first purification column that comprises aflibercept, the elution of the second purification column that comprises aflibercept, etc. The basis for comparison is variable, thus making a determination of what is included or excluded from the scope of the claims impossible. One embodiment can be included or excluded depending on which aflibercept composition is used for comparison. For examination purposes, claim 22 will be interpreted as a duplicate of claim 19. Correction is required.

16. Claim 23 (claims 24-30 dependent thereon) is indefinite in the recitation of “...(a) providing...(b) culturing... aflibercept; (c) harvesting.....” for the following reasons. In the absence of the term “and”, it is unclear if the method requires all three steps (a), (b) and (c), or if the method requires any of the steps (a), (b) or (c). If the intended method requires all the recited steps, the term “and” should be placed prior to step (c). Correction is required.

17. Claim 24 (claim 26 dependent thereon) is indefinite in the recitation of “wherein a titer of said host cells cultured in CDM to produce aflibercept is increased in comparison to a titer of host cells cultured in CDM exceeding one or more of said cumulative concentrations of (i)-(vi), while said sample color is no more yellow brown than...BY2...” for the following reasons. As written, it is unclear as to which is the titer being referred to by the term “a titer of cells...”. The term “a titer” implies a genus of titers. However, one cannot determine which are the titers encompassed by the claim. Usually, the term

“titer” refers to the concentration/amount of a particular compound, which in the case of cell culture, is related to a compound made by the cells in the cell culture. However, as written, it appears as if the term could refer to the concentration of cells. Does the titer refer to the number of cells or does the titer refer to the concentration/amount of aflibercept produced by the cells? Furthermore, the claim requires the titer comparison to be made with a genus of titers of host cells cultured using a genus of different CDMs in view of the fact that the term “exceeding one or more of said cumulative concentrations of (i)-(vi)” encompasses an entire genus of CDMs where each CDM comprises different concentrations of different compounds. For example, the cells can be cultured with a CDM having a cumulative concentration of nickel which is 1 mM, or a CDM having a cumulative concentration of copper that is 1 mM and a cumulative concentration of iron that is 1 mM. The basis for comparison is variable, making the determination as to what is encompassed and excluded from the claims impossible. An embodiment can be excluded if one uses a titer associated with a CDM having a cumulative concentration of nickel which is 1 mM, but encompassed by the claim if one uses a titer associated with a CDM having a cumulative concentration of copper that is 1 mM and a cumulative concentration of iron that is 1 mM. For examination purposes, it will be assumed that claims 24 and 26 are a duplicate of claim 23 as interpreted. Correction is required.

18. Claim 27 is indefinite in the recitation of “wherein said reduced sample color has a “b*” value that is reduced by about 45% compared to an aflibercept sample color obtained by harvesting aflibercept produced by said host cell forming a harvest comprising aflibercept wherein one or more concentration of (i) to (vi) are not maintained” for the following reasons. It is unclear as to what a “b*” value is and there is no reference or definition of what a “b*” value is in claim 23, from which claim 27 depends. Applicant argues that one of skill in the art would understand that the term b* refers to a value in the CIELAB color space and refers to the specification. This is not found persuasive. As set forth in MPEP § 2111.01 (II), it is improper to import limitations from the specification into a claim. In the absence of some statement indicating that the term “b*” is associated with a CIELAB color parameter, it is unclear as to how one

could assume that the term “b*” is unequivocally referring to one of the parameters of the CIELAB color space.

Furthermore, it is unclear as to which concentration of (i) to (vi) is not maintained. Items i-vi in claim 23 refer in part to concentrations that are less than or equal to value X. Thus, it is unclear if the term “concentration ...not maintained” refers to not maintaining the concentration of the different metal ions, anti-oxidants, and/or cysteine in the CDM at value X, or not maintaining the concentration of the different metal ions, anti-oxidants and cysteine in the CDM at values which are less or equal to value X. In addition, the term “obtained by harvesting aflibercept produced by said host cell forming a harvest comprising aflibercept” is unclear because one cannot determine how the term “forming a harvest comprising aflibercept” further limits the claim. Moreover, the claim requires the comparison to be made with a genus of colors in view of the fact that the aflibercept sample is obtained from culturing the host cell in a genus of CDMs by virtue of the fact that the claim requires a genus of combinations of different compounds and concentrations in the medium. The basis for comparison is variable, thus making a determination as to what is included or excluded from the scope of the claim impossible. An embodiment can be included or excluded from the scope of the claim depending on the CDM used to culture the host cell. For examination purposes, claim 27 will be assumed to be a duplicate of claim 23. Correction is required.

19. Claim 30 is indefinite in the recitation of “significant increase or decrease” for the following reasons. The term “significant increase or decrease” is a relative term not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In addition, there is no indication as to which is the product associated with the term “titer” (i.e., titer of what). If the titer is aflibercept titer, the claim should be amended accordingly. For examination purposes, claim 30 will be interpreted as a duplicate of claim 23. Correction is required.

20. When amending the claims, applicant is advised to carefully review all examined claims and make the necessary changes to ensure proper antecedent basis and dependency.

Claim Rejections - 35 USC § 102 (AIA)

21. Claims 1-30 remain rejected under 35 U.S.C. 102(a)(1) and 102(a)(2) as being anticipated by Johnson et al. (US Publication No. 2018/0223249 published 8/9/2018) as evidenced by Daly et al. (US Patent No. 7,396,664, issued 7/8/2008).

22. This rejection has been discussed at length in the prior Office action. It is maintained for the reasons of record and those set forth below.

23. Applicant argues that Johnson et al. do not specify whether taurine is included in the same concentration range when used in CDM. Applicant further argues that Johnson et al. do not teach whether the concentration of uridine and cysteine used in CDM are at the same concentration ranges. Applicant states that Johnson et al. only state that Table 1 shows the optional mixture of amino acids and are not necessarily present. Applicant states that cysteine is not necessarily added to CDM and instead may be used with serum-free media containing hydrolysates, citing paragraph [0020]. Applicant further states that Table 1 does not specify a particular protein. Applicant submits that aflibercept is merely disclosed as an optional protein and that Examples 1A and 1B refer to monoclonal antibodies which are not aflibercept. Applicant states that Johnson et al. do not teach producing and harvesting aflibercept in CDM having a target value of aflibercept variants, and that they do not teach whether aflibercept having a target value of aflibercept variants can be obtained by adding a cumulative concentration of an anti-oxidant in a CDM where the concentration ranges from about 0.001 mM to about 10 mM for any single anti-oxidant, or no more than 30 mM for all anti-oxidants in the CDM. Applicant argues that Johnson et al. do not teach a target value of aflibercept variants of less than about 20% that include oxidized aflibercept. Applicant states that Johnson et al. is silent with regard to producing and harvesting aflibercept having a color that is no more yellow brown than European Color Standard BY2 or a CIELAB color space as recited in the claims. Applicant states that the Examiner has previously admitted in the obviousness rejection that neither Johnson et al. nor Daly et al. disclose a method to reduce color intensities.

24. Applicant's arguments have been fully considered but not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the teachings of Johnson et al. and Daly et al. However, the Examiner disagrees with Applicant's assertions that the teachings of Johnson et al. as evidenced by Daly et al. do not anticipate the instant claims as written/interpreted. With regard to the argument that Johnson et al. do not specify whether taurine is included in the same concentration range when used in CDM, it is noted that paragraph [0059] of Johnson et al. states the following:

"[0059] The present invention provides a cell culture medium, which is serum-free, comprising about 0.1 mM to 10 mM taurine. "Serum-free" applies to a cell culture medium that does not contain animal sera, such as fetal bovine serum. The serum-free media may contain ≤ 16 g/L of hydrolysates, such as soy hydrolysate. The present invention also provides chemically defined media, which is not only serum-free, but also hydrolysate-free. "Hydrolysate-free" applies to cell culture media that contains no exogenous protein hydrolysates such as animal or plant protein hydrolysates such, for example peptones, tryptones and the like." (emphasis added)

Therefore, it is abundantly clear from the teachings of Johnson et al. indicated above that the range of 0.1 mM-10 mM taurine applies to any serum-free medium, including a chemically defined medium that is not only serum-free but also hydrolysate-free.

With regard to the argument that Johnson et al. do not teach whether the concentration of uridine and cysteine used in CDM are at the same concentration ranges, it is noted that Johnson et al. in paragraph [0059] as reproduced above, specifically states that their invention provides a cell culture medium which is serum-free, including a chemically defined medium that is serum-free and hydrolysate-free. As explained above, Johnson et al. specifically refers and defines a chemically defined medium as one of the embodiments of their invention. Paragraph [0069] of Johnson et al. states the following:

"[0069] In one embodiment, the media is further supplemented with about 170 μ M to 175 μ M nucleosides. In one embodiment, the media contains purine derivatives in a cumulative concentration of at least 40 μ M, at least 45 μ M, at least 50 μ M, at least 55 μ M, at least 60 μ M, at least 65 μ M, at least 70 μ M, at least 75 μ M, at least 80 μ M, at least 85 μ M, at least 90 μ M, at least 95 μ M, at least 100 μ M, or at least 105 μ M. In one embodiment, the media contains about 100 μ M to 110 μ M of purine derivatives. Purine derivatives include hypoxanthine and the nucleosides adenosine and guanosine. In one embodiment, the media contains pyrimidine derivatives in a cumulative concentration of at least 30 μ M, at least 35 μ M, at least 40

μM , at least 45 μM , at least 50 μM , at least 55 μM , at least 60 μM , or at least 65 μM . In one embodiment, the media contains about 65 μM to 75 μM of pyrimidine derivatives. Pyrimidine derivatives include the nucleosides thymidine, uridine, and cytidine. In one particular embodiment, the media contains adenosine, guanosine, cytidine, uridine, thymidine and hypoxanthine.” (emphasis added)

Therefore, it is abundantly clear that Johnson et al. teach that their serum-free media, including their chemically defined medium, comprises nucleosides, as specifically disclosed in paragraph [0069]. With regard to cysteine, paragraphs [0012], [0020] and [0021] of Johnson et al. are reproduced below:

“[0012] *In one embodiment*, the medium contains a base medium that is chemically defined, such as a custom formulation or a commercially available base medium. In one embodiment, the complete medium is chemically defined, free of sera and free of hydrolysate.” (emphasis added)

“[0020] In another aspect, the invention provides a method for cultivating cells in a cell culture medium, such as any embodiment of the medium described in the foregoing aspect. In one embodiment, the method employs the steps of propagating or maintaining a cell or cells in a medium that (1) contains taurine at a concentration of at least 0.1 mM.+-.0.015 mM, (2) contains $\leq .16$ g/L hydrolysate, or no hydrolysate, (3) is free of sera, (4) and optionally amino acids selected from the group consisting of a mixture of amino acids selected from Table 1.” (emphasis added)

“[0021] In one embodiment, the optional mixture of amino acid supplements are selected from the group consisting of the amino acids in Table 1:

TABLE 1

Amino acid	RANGE mM (mmol/L)	RANGE (g/L)
Alanine	0-11.2	0-1
Arginine	2.4-11.9	0.5-2.5
Asparagine	1.2-33.3	0.2-5
Aspartic Acid	1.8-93.9	0.2-32.5
Cysteine	1.1-19.9	0.2-3.5
Glutamic acid	1.4-47.6	0.2-7
Glutamine	0-23.9	0-3.5
Glycine	0-16.7	0-1.25
Histidine	1-9.5	0.2-2
Isoleucine	1.5-22.9	0.2-3
Leucine	1.5-38.1	0.2-5
Lysine	2.7-24.6	0.5-4.5
Methionine	1.3-13.4	0.2-2
Phenylalanine	1.2-18.2	0.2-3
Proline	1.7-28.1	0.2-5
Serine	1.9-57.1	0.2-6
Threonine	1.7-33.6	0.2-4
Tryptophan	0.5-16.7	0.1-3
Tyrosine	0.9-22.2	0.2-5
Valine	1.7-38.1	0.2-4

Paragraphs [0012], [0020] and [0059] clearly teach that a chemically defined medium is taught by Johnson et al. and that the ingredients and concentrations disclosed apply to their chemically defined medium. While it is agreed that the amino acids in Table 1 are optional, the fact is that Johnson et al. teach that any mixture of the amino acids recited in Table 1 can be present in their chemically defined medium. As such, Johnson et al. teach both a chemically defined medium that comprises any mixture of the amino acids listed in Table 1 at the concentrations shown as well as a chemically defined medium that does not comprise the amino acids listed in Table 1 at the concentrations shown. Therefore, contrary to Applicant's assertions, Johnson et al. teach a chemically defined medium that comprises uridine and cysteine at a concentration that is less than or equal to 10 mM (e.g., 1.1 mM).

With regard to the argument that cysteine is not necessarily added to CDM and instead may be used with serum-free media containing hydrolysates, citing paragraph [0020], or that Table 1 does not specify a particular protein, it is noted that (a) Table 1 is a table that provides amino acids as set forth in paragraph [0021] and is not expected to disclose proteins, and (b) nowhere in paragraph [0020], there is a statement excluding the presence of amino acids in chemically defined media. On the contrary, paragraph [0020] specifically and unequivocally refer to chemically defined media and how this chemically defined media can comprise any mixture of the amino acids set forth in Table 1. See paragraph [0020] reproduced above, particularly the section that has been emphasized.

With regard to the argument that aflibercept is merely disclosed as an optional protein and that Examples 1A and 1B refer to monoclonal antibodies which are not aflibercept, it is noted that while it is agreed that Johnson et al. do not provide a working example with aflibercept, the fact is that Johnson et al. specifically teach the production of aflibercept by cell culture using their chemically defined medium. Paragraph [0106] of Johnson et al. states:

“[0106] In some embodiments, the protein of interest is a recombinant protein that contains an Fc moiety and another domain, (e.g., an Fc-fusion protein). In some embodiments, an Fc-fusion protein is a receptor Fc-fusion protein, which contains one or more extracellular domain(s) of a receptor coupled to an Fc moiety. In some embodiments, the Fc moiety comprises a hinge region followed by a CH2 and CH3 domain of an IgG. In some embodiments, the receptor Fc-fusion protein contains two or more distinct

receptor chains that bind to either a single ligand or multiple ligands. For example, an Fc-fusion protein is a TRAP protein, such as for example an IL-1 trap (e.g., rilonacept, which contains the IL-1RAcP ligand binding region fused to the IL-1R1 extracellular region fused to Fc of hIgG1; see U.S. Pat. No. 6,927,004, which is herein incorporated by reference in its entirety), or a VEGF trap (e.g., aflibercept or ziv-aflibercept, which contains the Ig domain 2 of the VEGF receptor Flt1 fused to the Ig domain 3 of the VEGF receptor Flk1 fused to Fc of hIgG1; see U.S. Pat. Nos. 7,087,411 and 7,279,159). In other embodiments, an Fc-fusion protein is a ScFv-Fc-fusion protein, which contains one or more of one or more antigen-binding domain(s), such as a variable heavy chain fragment and a variable light chain fragment, of an antibody coupled to an Fc moiety.” (emphasis added)

Therefore, it is abundantly clear that an embodiment of the invention of Johnson et al. is the production of aflibercept with their media because they not only refer to aflibercept but they also incorporate by reference the patent that discloses aflibercept. As such, it is unclear as to how one could conclude that Johnson et al. do not teach the production of aflibercept with their chemically defined media.

With regard to the argument that Johnson et al. do not teach (a) producing and harvesting aflibercept in CDM having a target value of aflibercept variants by adding a cumulative concentration of an anti-oxidant in a CDM where the concentration ranges from about 0.001 mM to about 10 mM for any single anti-oxidant, or no more than 30 mM for all anti-oxidants in the CDM, (b) a target value of aflibercept variants of less than about 20% that include oxidized aflibercept, or (c) producing and harvesting aflibercept having a color that is no more yellow brown than European Color Standard BY2 or a CIELAB color space as recited in the claims, it is reiterated herein that those properties are inherent to the method of Johnson et al. *as evidenced by the teachings of the specification*. The specification of the instant application asserts that culturing host cells, such as CHO cells, that express aflibercept in CDM that comprises an antioxidant such as taurine at a concentration of 0.001 mM to 10 mM results in a reduction in the amount of aflibercept having oxidized amino acids, including the recited “less than about 20%”, wherein said oxidized amino acids are selected from methionine, tryptophan, histidine, phenylalanine, and tyrosine. The specification of the instant application also asserts that one could increase the titer of aflibercept without altering cell viability, ammonia or osmolality, by culturing a host

cell that expresses aflibercept in a CDM that comprises an anti-oxidant such as taurine at a concentration of 0.001 mM to 10 mM. If the CDM comprises taurine as the sole anti-oxidant, then the CDM of Johnson et al. (0.1 mM to 10 mM; paragraph [0063]) would meet the limitation regarding no more than 30 mM of total anti-oxidants. The specification further states that culturing the aflibercept producing cells in the presence of an anti-oxidant compound like taurine at the recited concentrations would result in an aflibercept sample having a color (i) no more yellow brown than European Color Standard BY2, or (ii) a yellow brown color characterized in the CIE L* a* b* color space as having an L* value of 70-99, an a* value of 0 and a b* value of 20 or less, at a concentration of 5 g/L of aflibercept less than 20% of aflibercept variants having oxidized amino acids. Therefore, it follows that the method of Johnson et al. would inherently result in a method that produces an aflibercept composition having the recited level of oxidized aflibercept variants, wherein the oxidation is at the recited amino acids, wherein the aflibercept composition has the recited color at a concentration of 5 g/L of aflibercept. As such, contrary to Applicant's assertions, the method of Johnson et al. anticipate the instant claims as written/interpreted.

25. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103 (AIA)

26. Claims 1-30 remain rejected under 35 U.S.C. 103 as being unpatentable over Johnson et al. (US Publication No. 2018/0223249 published 8/9/2018) as evidenced by Daly et al. (US Patent No. 7,396,664, issued 7/8/2008) in view of Vijayasankaran et al. (US Publication No. 2013/0281355 published 10/24/2013).

27. This rejection has been discussed at length in the prior Office action. It is maintained for the reasons of record and those set forth below.

28. Applicant argues that Vijayasankaran et al. merely states that it is believed that the use of particular medium components at certain concentrations produce a polypeptide drug product with acceptable quality attributes without suggesting particular limitations on the cumulative combinations. Applicant states that Table 1 of Vijayasankaran et al. includes many supplements and concentration ranges that teach away from the claimed invention. Applicant states that Vijayasankaran et al. do not provide guidance on where to begin and describes a near infinite number of combinations of supplements and concentration ranges, and would not have been combined with Johnson et al. Applicant cites paragraphs [0331] and [0338] in support of the argument that Vijayasankaran et al. teach that color reduction was achieved by reducing titer which is contrary to the claimed invention. Applicant states that Vijayasankaran et al. teach that the use of CDM is not necessary and that neither Vijayasankaran et al. nor Johnson et al. teach or suggest the color limitations recited in the claims. Applicant states that Vijayasankaran et al. teach the use of catalase which has a selective effect on color where higher concentrations of iron are used, thus proposing alternative methods for mitigating color rather than reducing iron below 75 μM (paragraph [0339]). Applicant further argues that Vijayasankaran et al. do not describe a total concentration of all antioxidants less than 30 mM and do not mention taurine or hydrocortisone, thus not suggesting that the use of antioxidants reduce color or acidic variants.

29. Applicant's arguments have been fully considered but not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the teachings of Vijayasankaran et al. and Johnson et al. However, the Examiner disagrees with Applicant's assertions that the claimed invention is not obvious over the teachings of Vijayasankaran et al. and Johnson et al. With regard to the argument that Vijayasankaran et al. (a) merely states that it is believed that the use of particular medium components at certain concentrations produce a polypeptide drug product with acceptable quality attributes without suggesting particular limitations on the cumulative combinations, (b) provide a Table that includes many supplements and concentration ranges that teach away from the claimed invention, and (c) do not provide guidance on where to begin and describes a near infinite number of combinations of supplements and concentration ranges, and would not have been combined with Johnson et al., it is noted that Table 1

provides seven components that could be added to their media, namely cysteine, vitamin B2, vitamin B6, vitamin B9, vitamin B12, ferric citrate, and hydrocortisone. Therefore, while there are several concentrations listed for each of these compounds, the number of combinations of components is not infinite but rather well-defined. Even if the argument is made that the number of combinations of these seven compounds and the concentrations listed in Table 1 is extensive, it is noted that Vijayasankaran et al. provides more guidance as to the components and concentrations that are beneficial to reduce color intensity and reduce oxidized variants. Paragraph [0152] of Vijayasankaran et al. states:

“[0152] Methods for reducing the presence of charge variants (e.g., acidic charge variants) are provided, as are compositions comprising a reduced level of charge variants (e.g., acidic charge variants), wherein the media detailed herein reduces the presence of charge variants when used in a method of producing a polypeptide as compared to charge variants obtained when the polypeptide is produced in a different media. In one variation, the media is a chemically defined cell culture medium comprising from about from about 300 mg/L to about 1200 mg/L cysteine, from about 2 μ M to about 80 μ M ferric citrate, and from about 0.05 μ M to about 0.5 μ M hydrocortisone. In a variation, the chemically defined culture medium further comprises vitamin B2, vitamin B6, vitamin B9 and vitamin B12. In a variation the vitamin B2 is at a concentration from about 0.05 mg/L to about 1.0 mg/L. In another variation, vitamin B2 is at a concentration of from about 0.05 mg/L to about 0.50 mg/L. In another variation, vitamin B2 is at a concentration of from about 0.05 mg/L to about 0.40 mg/L. In another variation, vitamin B2 is at a concentration of from about 0.05 mg/L to about 0.30 mg/L. In a further variation the vitamin B6 is at a concentration from about 0.05 mg/L to about 10.0 mg/L. In a further variation, vitamin B6 is at a concentration of from about 0.05 mg/L to about 8.0 mg/L. In a further variation, vitamin B6 is at a concentration of from about 0.05 mg/L to about 7.0 mg/L. In a further variation, vitamin B6 is at a concentration of from about 0.05 mg/L to about 6.0 mg/L. In any of the variations herein the vitamin B6 is at a concentration from about 0.05 mg/L to about 10.0 mg/L, from about 0.05 mg/L to about 8.0 mg/L, from about 0.05 mg/L to about 7.0 mg/L or from about 0.05 mg/L to about 6.0 mg/L. In a further variation the vitamin B9 is at a concentration from about 0.05 mg/L to about 12.0 mg/L. In any of the variations herein the vitamin B9 is at a concentration from about 0.05 mg/L to about 12.0 mg/L. In a further variation the vitamin B 12 is at a concentration from about 0.05 mg/L to about 2.5 mg/L. In any of the variations herein the vitamin B 12 is at a concentration from about 0.05 mg/L to about 2.5 mg/L.” (emphasis added)

Therefore, it is clear from the teachings of Vijayasankaran et al. that they disclose a CDM wherein the concentration and the ingredients are clearly defined and the combinations limited to a few combinations, including an iron concentration of about 2 μ M to about 80 μ M and a hydrocortisone

concentration of 0.05 μM to about 0.5 μM . As such, at a minimum, one of skill in the art would conclude that Vijayasankaran et al. provide a starting point with regard to iron and hydrocortisone. Please note that Vijayasankaran et al. teach that their CDM can lack vitamin B2, vitamin B6, vitamin B9 and vitamin B12. In view of this, one of skill in the art would conclude that at a minimum Vijayasankaran et al. disclose a CDM where iron and hydrocortisone concentrations were clearly defined.

With regard to the argument that Vijayasankaran et al. teach that color reduction was achieved by reducing titer which is contrary to the claimed invention, it is noted that the teachings of Johnson et al. clearly teach that taurine is added to CDM to increase the titer of the protein of interest. Therefore, if Vijayasankaran et al. teach how one could obtain color intensity reduction and Johnson et al. teach how to increase titer, it would be obvious to one of skill in the art to produce aflibercept using taurine as a media component to increase aflibercept titers, taught by Johnson et al., as well the media components disclosed by Vijayasankaran et al. to reduce color intensity.

With regard to the argument that Vijayasankaran et al. teach that the use of CDM is not necessary, it is reiterated herein that Vijayasankaran et al. teach a CDM medium as set forth at least in paragraph [0152] as reproduced above. While it may be that Vijayasankaran et al. teach that their medium can be chemically undefined, the fact is that Vijayasankaran et al. specifically teach a CDM medium as well as a chemically undefined medium to practice their method. It should also be noted that the instant application is an obviousness rejection based on the combined teachings of the prior art. As previously indicated, Johnson et al. also teach a chemically defined medium. Therefore, whether Vijayasankaran et al. teach a chemically undefined medium or not is irrelevant to the instant discussion when the analysis is based on the combined teachings of Johnson et al. and Vijayasankaran et al. and both Johnson et al. and Vijayasankaran et al. teach a chemically defined medium as set forth at least in paragraph [0152].

With regard to the argument that Vijayasankaran et al. teach the use of catalase which has a selective effect on color where higher concentrations of iron are used, thus proposing alternative methods for mitigating color rather than reducing iron below 75 μM , Applicant's attention is directed to paragraphs [0335], [0338], and [0339] reproduced below:

[0335] To assess the contribution of iron levels on color intensity of isolated antibody, the level of iron was varied while the other media component levels were kept constant. The media was prepared as described in Example 2. Media components that were varied for this study were not included in the blended powders but added separately at appropriate levels during media preparation. Basal Media 1 was reformulated to have reduced levels of ferrous sulfate in order to produce basal Media 12 containing 18 μM ferrous sulfate and basal Media 13 containing 10 μM ferrous sulfate. For production of monoclonal IgG1 antibody (anti-Beta7) from CHO cells, the cell culture was fed with basal Media 1 and feed Media 2, basal Media 12 and feed Media 2, or basal Media 13 and feed Media 2 in fed-batch mode. Cell viability measurements and isolation of the monoclonal IgG1 antibody was performed as described in Example 2. After antibody purification, antibody titers were determined as described in Example 2. Color intensity was determined with a color assay wherein higher numerical values indicate higher color intensity and lower numerical values indicate lower color intensity. This color assay, also referred to as the NIFTY assay, was implemented as described in Example 3. Analysis of packed cell volume over time (IVPCV) and antibody titer levels with JMP 8.0.2 statistical software demonstrated that although cell viability and antibody titer levels were reduced with lower iron concentration levels as compared to iron at a concentration of 75 μM (FIGS. 5A and B), lower iron concentration in the cell culture media significantly decreased color intensity in the isolated antibody (FIG. 5C).” (emphasis added) .

“[0338] Reduced vitamin B levels and reduced iron concentrations were combined to test whether the beneficial effects on color due to vitamins and iron were additive. Basal Media 13, Media 14, Media 15, and Media 16 were reformulated to have reduced levels of vitamin B levels in order to produce basal Media 21, Media 22, Media 23, and Media 25, respectively. Additionally, basal Media 1 was reformulated to have reduced vitamin B levels and 10 μM ferric nitrate as the iron source in order to produce basal Media 24. Reduced vitamin levels for Media 21 through 25 were as follows: 0.25 mg/L vitamin B2, 5.35 mg/L vitamin B6 (5.35 mg/L pyridoxine+0 mg/L pyridoxal), 8.61 mg/L vitamin B9, and 1.76 mg/L vitamin B12. For production of monoclonal IgG1 antibody from CHO cells, the cell culture was fed with basal Media 21, 22, 23, 24, or 25 and with feed Media 2 in fed-batch mode. Isolation of the monoclonal IgG1 antibody and measurement of antibody titers was performed as described in Example 2. Color intensity was measured with the NIFTY assay. *Analysis of antibody titer levels and color intensity demonstrated that when the ferrous sulfate concentration was lowered from the 75 μM to 18 μM and combined with lower vitamin concentrations, the resulting color and titer were lower than when reducing one of the factors alone* (FIGS. 6D and E, plus signs). However, there appeared to be no further benefit in reducing iron concentration from 18 μM to 10 μM for either ferric nitrate or ferrous sulfate (FIGS. 6D and E, plus signs).” (emphasis added)

“[0339] To investigate the contribution of reactive oxygen species (ROS) to antibody color intensity, in vitro experiments were performed by spiking a 2 g/L sample of monoclonal IgG1 antibody into a vial

containing cell culture media supplemented with 75 μM or 18 μM ferrous sulfate. Additional in vitro experiments were performed by spiking a 2 g/L sample of monoclonal IgG1 antibody (anti-Beta7) into a vial containing cell culture media supplemented with 1.41 mg/L vitamin B2 or 0.25 mg/L vitamin B2. The samples were incubated at 37.degree. C. for 5 days without any cells in the absence or presence of 203 U/ml catalase. Color intensity was determined with a color assay wherein higher numerical values indicate higher color intensity and lower numerical values indicate lower color intensity. This color assay, also referred to as the NIFTY assay, was implemented as described in Example 3. Analysis of color levels with JMP 8.0.2 statistical software demonstrated that while increased levels of iron increased color intensity of the antibody solution (FIG. 7A) *this increase in color was reduced by addition of catalase* (FIG. 7B; middle trend line). In contrast, although increased levels of vitamin B2 increased color intensity of the antibody solution, *the color intensity was not reduced by addition of catalase* (FIGS. 7A and B; middle trend line).” (emphasis added)

As set forth in paragraphs [0335] and [0338], it is abundantly clear that Vijayasankaran et al. provides a well-defined iron concentration that would result in a reduction in color intensity and also provides clear guidance as to the effect of vitamins on color. Vijayasankaran et al. teach that by using ferric citrate so that the iron concentration is between 10-20 μM results in the lowest color index number (Figure 12A). While Applicant argues that Vijayasankaran et al. teach the addition of catalase to reduce color intensity as another method, it is noted that the addition of catalase was not taught as a method to reduce color but rather as a method to determine the contribution of reactive oxygen species to antibody color intensity. As stated in paragraph [0339], last sentence, the color intensity was not reduced by addition of catalase when the color intensity increase was due to increased levels of vitamin B2. Therefore, contrary to Applicant’s assertions, Vijayasankaran et al. do not teach the use of catalase to decrease color intensity. Instead, Vijayasankaran et al. specifically disclose the advantageous effect of using a particular iron concentration in reducing color intensity.

With regard to the argument that Vijayasankaran et al. do not describe a total concentration of all antioxidants less than 30 mM and do not mention taurine or hydrocortisone, thus not suggesting that the use of antioxidants reduce color or acidic variants, Applicant is reminded that the instant rejection is an obviousness rejection which is based on the combined teachings of the prior art. In the instant case, the concentration of taurine is provided by Johnson et al. who clearly teach that taurine is beneficial to

increase titers. It is reiterated herein that Vijayasankaran et al. teach hydrocortisone in their CDM at levels of 0.05 μM to about 0.5 μM as set forth at least in paragraph [0152] reproduced above. Therefore, the levels of taurine (0.1-10 mM) and hydrocortisone (e.g. about 0.5 μM) taught by Johnson et al. and Vijayasankaran et al., respectively, are not believed to exceed the requirement of no more than 30 mM of anti-oxidants. Applicant's arguments regarding a suggestion that the use of antioxidants reduce color or acidic variants is not found persuasive because paragraph [0345] as disclosed by Vijayasankaran et al. states:

“[0345] The correlation of color intensity and formation of acidic charge variants in antibodies isolated from cell lines cultured with cell media containing increasing concentrations of iron from different sources was examined. For production of monoclonal IgG1 antibody (anti-Beta7) from CHO cells, the cells were cultured with basal Media 1 containing 75 μM ferrous sulfate, basal Media 12 containing 18 μM ferrous sulfate or basal Media 13 containing 10 μM ferrous sulfate in fed-batch mode. Additional cell cultures were fed basal Media 15 containing 18 μM ferric citrate or basal Media 16 containing 10 μM ferric citrate. All cell cultures were fed iron-free feed media in fed-batch mode. Color intensity was determined using the NIFTY assay as described in Example 3. The greatest reduction in color intensity was seen in antibodies isolated from cells cultured with basal media containing reduced levels of iron (FIG. 12A). Reduced color intensity correlated with a reduced presence of acidic charge variants in the isolated antibody solution (FIG. 12B). “ (emphasis added)

It is clear from the teachings of Vijayasankaran et al. that the media component that allows a greater reduction in color intensity is iron and that there is a correlation between color intensity and the presence of acidic charge variants. Therefore, a suggestion that the use of antioxidants reduce color or acidic variants is irrelevant to the instant discussion because Vijayasankaran et al. clearly states that it is iron the media component that appears to have the biggest impact in the reduction of color intensity, and consequently in the reduction of acidic charge variants. Thus, even if antioxidants were to have an effect on color intensity, one of skill in the art did not need to know such correlation to combine the teachings of Vijayasankaran et al. regarding iron and the teachings of Johnson et al. to obtain an aflibercept composition with a reduced color intensity.

With regard to the argument that neither Vijayasankaran et al. nor Johnson et al. teach or suggest the color limitations recited in the claims, it is noted that as explained above and in the prior Office action, the method of Johnson et al. results in the production of an aflibercept composition comprising the recited color limitations in view of the fact that the specification asserts that a method as described by Johnson et al. would produce an aflibercept composition having the recited color characteristics at a concentration of 5 g/L of aflibercept. If the presence of iron at the concentrations taught by Vijayasankaran et al. reduces color intensity, and the method of Johnson et al. already produces a composition with the desired color characteristics, there is a reasonable expectation of success in obtaining an aflibercept composition having a color intensity which is slightly lower than the aflibercept composition of Johnson et al. alone. Therefore, contrary to Applicant's assertions, the color limitations recited in the claims are met by the teachings of Johnson et al. alone or in combination with the teachings of Vijayasankaran et al. As such, for the reasons of record and those set forth above, the claimed invention is deemed obvious over the prior art of record.

30. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Conclusion

31. No claim is in condition for allowance.

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

33. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

34. Applicant is advised that any Internet email communication by the Examiner has to be authorized by Applicant in written form. See MPEP § 502.03 (II). Without a written authorization by Applicant in place, the USPTO will not respond via Internet email to any Internet correspondence which contains information subject to the confidentiality requirement as set forth in 35 U.S.C. 122. Sample written authorization language can be found in MPEP § 502.03 (II). An Authorization for Internet Communications in a Patent Application or Request to Withdraw Authorization for Internet Communications form (SB/439) can be found at <https://www.uspto.gov/patent/forms/forms-patent-applications-filed-or-after-september-16-2012>, which can be electronically filed.

35. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) 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>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DELIA M RAMIREZ, Ph.D., whose telephone number is (571) 272-0938. The examiner

can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (408) 918-7584. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/DELIA M RAMIREZ/
Primary Examiner, Art Unit 1652

DR
March 20, 2021

<i>Index of Claims</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	10/10/2020	11/22/2020	03/20/2021						
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	2	÷	✓	✓						
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Search Notes 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

CPC - Searched*		
Symbol	Date	Examiner
C07K14/71; C12P21/02; C07K2319/30	11/27/2020	DR

CPC Combination Sets - Searched*		
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Search Notes		
Search Notes	Date	Examiner
STN- index bioscience medicine - see search history and entire transcript	11/27/2020	DR
WEST- USPT, PGPB, DWPI, EPAB, JPAB- see search history	11/27/2020	DR
PALM- inventor search-Shawn Lawrence, Amy Johnson, Meghan Casey, Jaimie Mastrogiacono, Shunhai Wang, Ning Li	11/27/2020	DR
parent cases considered-63/065,012	11/27/2020	DR
STN/WEST-updated search of 11/27/2020	03/20/2021	DR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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	Examiner DELIA M RAMIREZ	Art Unit 1652

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		16996030
	Filing Date		2020-08-18
	First Named Inventor	Shawn Lawrence	
	Art Unit	1652	
	Examiner Name	Delia M. Ramirez	
	Attorney Docket Number	070816-02250	

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↓	2	20180326126	A1	2018-11-15	Bernd Fiedler	
↓	3	20080242587	A1	2008-10-02	Kim Hak-Zoo	

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/D.R./	1	WO2014/145098	WO	A1	2014-09-18	Genentech Inc. [US]		☐

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/D.R/	2	WO2018/116198	WO	A1	2018-06-28	Serum Institute of India Private Ltd. [IN]		☐
	3	WO2019/178151	WO	A1	2019-09-19	Amgen Inc. [US]		☐
	4	WO2017/129685	WO	A1	2017-08-03	Formycon AG [DE]		☐
	5	WO2016/128559	WO	A1	2016-08-16	Hansa Medical AB [SE]		☐
	6	EP 3256580	EP	A1	2017-12-20	Hansa Medical AB [SE]	Equivalent to WO2016/128558A1	☐
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/D.R/	1	Florian Krattenmacher: "Beyond chemically defined - Characterization of chemically defined cell culture medium for the cultivation of CHO cells", 1 December 2019 (2019-12-01), ~~XP055766822~~ , Retrieved from the Internet: URL:https://pub.uni-bielefeld.de/download/2943695/2944336/FKrattenmacher 2020_Beyond ChemicallyDefinedCharacterizatiofCDM PhD Thesis.pdf; retrieved on 2021-01-10 [retrieved on 2021-01-1	☐
	2	Unknown: "Assessment report Eylea aflibercept Procedure No.: EMEA/H/C/002392/", 20 September 2012 (2012-09-20), ~~XP055766333~~ , Retrieved from the Internet:URL:https://www.ema.europa.eu/en/documents/assessment-report/eylea-epar-public-assessment-report en.pdf [retrieved on 2021-01-18] paragraph [2.2.2]	☐
	3	RYAN J. GRAHAM ET AL: "Consequences of trace metal variability and supplementation on Chinese hamster ovary (CHO) cell culture performance: A review of key mechanisms and considerations", BIOTECHNOLOGY AND BIOENGINEERING, vol. 116, no. 12, 30 August 2019 (2019-08-30), pages 3446-3456	☐

/DELIA M RAMIREZ/ 03/18/2021

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SEA (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S)
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122 FILE ADISCTI
6 FILE ADISINSIGHT
32 FILE AGRICOLA
48 FILE BIOSIS
105 FILE BIOTECHABS
105 FILE BIOTECHDS
42 FILE BIOTECHNO
31 FILE CABA
77 FILE CAPLUS
12 FILE CEABA
31 FILE DDFU
315 FILE DGENE
56 FILE DRUGU
61 FILE EMBASE
109 FILE ESBIODBASE
15 FILE FSTA
4 FILE GENBANK
885 FILE IFIAL
1 FILE IMSRESEARCH
1 FILE KOSMET
46 FILE MEDLINE
1 FILE NTIS
83 FILE PQSCITECH
45 FILE SCISEARCH
62 FILE TOXCENTER
1392 FILE USPATFULL
3 FILE USPATOLD
656 FILE USPAT2
11 FILE IPA
L1 QUE (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S)
(COLOR? OR COLOU?)
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D RANK
FILE 'USPATFULL, IFIAL, USPAT2, ADISCTI, ESBIODBASE, BIOTECHDS,
PQSCITECH, CAPLUS, TOXCENTER, EMBASE, DRUGU, BIOSIS, MEDLINE, SCISEARCH,
BIOTECHNO, AGRICOLA, CABA' ENTERED AT 20:43:51 ON 20 MAR 2021
L2 3852 SEA (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S)
(COLOR? OR COLOU?)
L3 331 SEA L2(S) (IRON? OR FERROU? OR FERRIC? OR ZINC? OR "ZN" OR
COPPE? OR "CU" OR NICKE? OR "NI" OR CYSTEIN? OR "CYS" OR
"ANTI-OXIDANT" OR ANTIOXIDAN? OR HYDROCORTISO?)
L4 15 SEA L3(S) ((MEDIA? OR MEDIUM?) (20A) (DEFINE?))
L5 15 DUP REM L4 (0 DUPLICATES REMOVED)
D IBIB ABS L5 1-15
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		16996030
	Filing Date		2020-08-18
	First Named Inventor	Shawn Lawrence	
	Art Unit	1652	
	Examiner Name	Delia M. Ramirez	
	Attorney Docket Number	070816-02250	

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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	1					

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FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
/D.R./	1	WO2014/020160	WO	A1	2014-02-06	Sanofi SA [FR]		☐

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NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵

/DELIA M RAMIREZ/ 03/18/2021

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	16996030
Filing Date	2020-08-18
First Named Inventor	Shawn Lawrence
Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	070816-02250

/D.R./	1	NIKA KRULJEC ET AL: "Alternative Affinity Ligands for Immunoglobulins," BIOCONJUGATE CHEMISTRY, vol. 28, no. 8, 16 August 2017 (2017-08-16), pages 2009-2030	☐
/D.R./	2	Unknown: "Antibody Affinity Resins," 28 September 2018 (2018-09-28), XP055771552, Retrieved from the Internet: URL:https://www.thermofisher.com/documentconnect/document-connect.html?url=https%3A%2F%2Fassets.thermofisher.com%2FTFS-Assets%2FLSG%2Fmanuals%2FMAN0017191_CapSelectAntibodyAffinityResins.PI.pdf&tifle=UNJvalVjdCBJbmZvIFNoZWV0i6DVXBOdXJ1U2VsZWNOIEFudG1ib2R5IEFmZmluaXR5IFJ1c21ucw== [retrieved on 2021-02-02]	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/DELIA M RAMIREZ/	Date Considered	03/18/2021
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		16996030	
	Filing Date		2020-08-18	
	First Named Inventor	Shawn Lawrence		
	Art Unit	1652		
	Examiner Name	Delia M. Ramirez		
	Attorney Docket Number	070816-02250		

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/D.R./	1	6309862	B1	2001-10-30	Mats Jarekrans et al.	
/D.R./	2	7396664	B2	2008-07-08	Thomas J. Daly	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/D.R./	1	20140273095	A1	2014-09-18	Oshodi Shadia Abike et al.	
/D.R./	2	20180223249	A1	2018-08-09	Amy S. Johnson et al.	
/D.R./	3	20130281355	A1	2013-10-24	Natarajan Vijayasankaran et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
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/DELIA M RAMIREZ/

03/18/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16996030
Filing Date	2020-08-18
First Named Inventor	Shawn Lawrence
Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	070816-02250

/D.R/	1	WO2002/101019	WO	A2	2002-12-19	Genentech Inc.		☐
	2	WO2016/156476	WO	A1	2016-10-06	Boehringer Ingelheim International GMBH		☐
	3	WO202/0229584	WO	A1	2020-11-19	Formycon AG		☐
	4	WO2018/094316	WO	A1	2018-05-24	Just Biotherapeutics, Inc.		☐
	5	WO2017/168296	WO	A1	2017-10-05	Navya Biologicals Pvt. Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
/D.R/	1	ZAHRA SHEIKHOESLAMI ET AL: "Elucidating the effects of postinduction glutamine feeding on the growth and productivity of CHO cells," BIOTECHNOLOGY PROGRESS, vol. 30, no. 3, 1 May 2014 (2014-05-01), pages 535-546	☐
/D.R/	2	KIM DO YUN ET AL: "Fed-batch CHO cell t-PA production and feed glutamine replacement to reduce ammonia production," BIOTECHNOLOGY PROGRESS, WILEY-BLACKWELL PUBLISHING, INC., US, vol. 29, no. 1, 1 January 2013, pages 165-175	☐
/D.R/	3	PING XU ET AL: "Effects of glutamine and asparagine on recombinant antibody production using CHO-GS cell lines," BIOTECHNOLOGY PROGRESS, vol. 30, no. 6, 8 November 2014, pages 1457-1468	☐

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/DELIA M RAMIREZ/ 03/18/2021

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	16996030
Filing Date	2020-08-18
First Named Inventor	Shawn Lawrence
Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	070816-02250

EXAMINER SIGNATURE

Examiner Signature	/DELIA M RAMIREZ/	Date Considered	03/18/2021
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

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FILE 'HOME' ENTERED AT 20:39:57 ON 20 MAR 2021

=> index bioscience medicine

FILE 'WPIDS' ACCESS NOT AUTHORIZED
FILE 'WPINDEX' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHABS,
BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA, CIN, CROPB, CROPU, DDFB, DDFU,
DGENE, DRUGB, DRUGU, EMBASE, ESBIODBASE, FSTA, GENBANK, IFIALL,
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21

43 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (COLOR? OR COLOU?)

("CHO" IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.

For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (COLOR? OR COLOU?
)

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122 FILE ADISCTI
6 FILE ADISINSIGHT
32 FILE AGRICOLA
48 FILE BIOSIS
105 FILE BIOTECHABS
105 FILE BIOTECHDS
42 FILE BIOTECHNO
31 FILE CABA
77 FILE CAPLUS
12 FILE CEABA
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56 FILE DRUGU
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20 FILES SEARCHED...

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61 FILE EMBASE
109 FILE ES BIOBASE
15 FILE FSTA
4 FILE GENBANK
885 FILE IFIALL
1 FILE IMSRESEARCH
1 FILE KOSMET
46 FILE MEDLINE
1 FILE NTIS
83 FILE PQSCITECH
45 FILE SCISEARCH
62 FILE TOXCENTER
1392 FILE USPATFULL
3 FILE USPATOLD
656 FILE USPAT2
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40 FILES SEARCHED...

11 FILE IPA

29 FILES HAVE ONE OR MORE ANSWERS, 43 FILES SEARCHED IN STNINDEX

L1 QUE (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (COLOR? OR
COLOU?)

=> d rank

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F1 1392 USPATFULL
F2 885 IFIALL
F3 656 USPAT2
F4 315 DGENE
F5 122 ADISCTI
F6 109 ES BIOBASE
F7 105 BIOTECHABS
F8 105 BIOTECHDS
F9 83 PQSCITECH
F10 77 CAPLUS
F11 62 TOXCENTER
F12 61 EMBASE
F13 56 DRUGU
F14 48 BIOSIS
F15 46 MEDLINE
F16 45 SCISEARCH
F17 42 BIOTECHNO
F18 32 AGRICOLA
F19 31 CABA
F20 31 DDFU
F21 15 FSTA
F22 12 CEABA
F23 11 IPA
F24 6 ADISINSIGHT
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F25	4	GENBANK
F26	3	USPATOLD
F27	1	IMSRESEARCH
F28	1	KOSMET
F29	1	NTIS

=> file f1-f3 f5-f19

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	11.22	11.43

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=> s (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (COLOR? OR COLOU?
)

L2 3852 (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S) (COLO
R? OR COLOU?)

=> s l2(s)(IRON? OR FERROU? OR FERRIC? OR ZINC? OR "ZN" OR COPPE? OR "CU" OR NICKE
? OR "NI" OR CYSTEIN? OR "CYS" OR "ANTI-OXIDANT" or antioxidan? or hydrocortiso
?)

L3 331 L2(S)(IRON? OR FERROU? OR FERRIC? OR ZINC? OR "ZN" OR COPPE?
OR "CU" OR NICKE? OR "NI" OR CYSTEIN? OR "CYS" OR "ANTI-OXIDANT"
OR ANTIOXIDAN? OR HYDROCORTISO?)

=> s l3(s)((MEDIA? OR MEDIUM?) (20A)(DEFINE?))

L4 15 L3(S)((MEDIA? OR MEDIUM?) (20A)(DEFINE?))

=> dup rem l4

PROCESSING COMPLETED FOR L4

L5 15 DUP REM L4 (0 DUPLICATES REMOVED)

=> d ibib abs l5 1-15

L5 ANSWER 1 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2021:20492 USPATFULL Full-text

TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS
FOR POLYPEPTIDE PRODUCTION

INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA,
UNITED STATES
MEIER, Steven J., South San Francisco, CA, UNITED
STATES
VARMA, Sharat, South San Francisco, CA, UNITED STATES
YANG, Yi, South San Francisco, CA, UNITED STATES

PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20210017488	A1	20210121
APPLICATION INFO.:	US 2020-17063322	A1	20201005 (17)
RELATED APPLN. INFO.:	Division of Ser. No. US 2018-16151904, filed on 4 Oct 2018, Pat. No. US 10829732 Division of Ser. No. US 2015-14852311, filed on 11 Sep 2015, Pat. No. US 10131873 Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING Continuation of Ser. No. US 2013-61799602, filed on 15 Mar 2013, PENDING		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	102		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	11 Drawing Page(s)		
LINE COUNT:	4255		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are
methods of using the media for cell culturing and polypeptide production
from cells. Compositions comprising polypeptides, such as therapeutic
polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 2 OF 15 USPAT2 on STN

ACCESSION NUMBER: 2019:166288 USPAT2 Full-text

TITLE: Cell culture compositions with antioxidants and methods
for polypeptide production

INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,
UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED
STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES

PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES

(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10829732	B2	20201110
APPLICATION INFO.:	US 2018-16151904		20181004 (16)
RELATED APPLN. INFO.:	Division of Ser. No. US 2015-14852311, filed on 11 Sep 2015, Pat. No. US 10131873 Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	22	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 11 Drawing Page(s)	
LINE COUNT:	4261	

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

L5 ANSWER 3 OF 15 USPAT2 on STN

ACCESSION NUMBER: 2019:3991 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA, UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10676710	B2	20200609
APPLICATION INFO.:	US 2018-15997342		20180604 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14211416, filed on 14 Mar 2014, Pat. No. US 10017732		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	32	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)	
LINE COUNT:	4173	

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

L5 ANSWER 4 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2019:166288 USPATFULL Full-text
TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS FOR POLYPEPTIDE PRODUCTION
INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA, UNITED STATES

MEIER, Steven J., South San Francisco, CA, UNITED STATES
VARMA, Sharat, South San Francisco, CA, UNITED STATES
YANG, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190144817	A1	20190516
	US 10829732	B2	20201110
APPLICATION INFO.:	US 2018-16151904	A1	20181004 (16)
RELATED APPLN. INFO.:	Division of Ser. No. US 2015-14852311, filed on 11 Sep 2015, Pat. No. US 10131873 Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	27	
EXEMPLARY CLAIM:	1-64	
NUMBER OF DRAWINGS:	11 Drawing Page(s)	
LINE COUNT:	3948	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2019:3991 USPATFULL Full-text
TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS FOR POLYPEPTIDE PRODUCTION
INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA, UNITED STATES
MEIER, Steven J., South San Francisco, CA, UNITED STATES
VARMA, Sharat, South San Francisco, CA, UNITED STATES
YANG, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190002822	A1	20190103
	US 10676710	B2	20200609
APPLICATION INFO.:	US 2018-15997342	A1	20180604 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14211416, filed on 14 Mar 2014, Pat. No. US 10017732		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	37	
EXEMPLARY CLAIM:	1-63	
NUMBER OF DRAWINGS:	9 Drawing Page(s)	
LINE COUNT:	3852	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 15 USPAT2 on STN

ACCESSION NUMBER: 2016:3643 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods
for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,
UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED
STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10131873	B2	20181120
APPLICATION INFO.:	US 2015-14852311		20150911 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail A	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 11 Drawing Page(s)	
LINE COUNT:	4275	

AB Cell culture media comprising antioxidants are provided herein as are
methods of using the media for cell culturing and polypeptide production
from cells. Compositions comprising polypeptides, such as therapeutic
polypeptides, produced by the methods herein are also provided.

L5 ANSWER 7 OF 15 USPAT2 on STN

ACCESSION NUMBER: 2014:352125 USPAT2 Full-text
TITLE: Cell culture compositions with antioxidants and methods
for polypeptide production
INVENTOR(S): Vijayasankaran, Natarajan, South San Francisco, CA,
UNITED STATES
Meier, Steven J., South San Francisco, CA, UNITED
STATES
Varma, Sharat, South San Francisco, CA, UNITED STATES
Yang, Yi, South San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 10017732	B2	20180710
APPLICATION INFO.:	US 2014-14211416		20140314 (14)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Belyavskiy, Michail	
LEGAL REPRESENTATIVE:	Morrison &, Foerster LLP	
NUMBER OF CLAIMS:	24	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)	
LINE COUNT:	4101	

AB Cell culture media comprising antioxidants are provided herein as are
methods of using the media for cell culturing and polypeptide production
from cells. Compositions comprising polypeptides, such as therapeutic
polypeptides, produced by the methods herein are also provided.

L5 ANSWER 8 OF 15 USPATFULL on STN
 ACCESSION NUMBER: 2016:3643 USPATFULL Full-text
 TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS
 FOR POLYPEPTIDE PRODUCTION
 INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA,
 UNITED STATES
 MEIER, Steven J., South San Francisco, CA, UNITED
 STATES
 VARMA, Sharat, South San Francisco, CA, UNITED STATES
 YANG, Yi, South San Francisco, CA, UNITED STATES
 PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160002593	A1	20160107
	US 10131873	B2	20181120
APPLICATION INFO.:	US 2015-14852311	A1	20150911 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2014-US29772, filed on 14 Mar 2014, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	101	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	11 Drawing Page(s)	
LINE COUNT:	4302	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are
 methods of using the media for cell culturing and polypeptide production
 from cells. Compositions comprising polypeptides, such as therapeutic
 polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 9 OF 15 USPATFULL on STN
 ACCESSION NUMBER: 2014:352125 USPATFULL Full-text
 TITLE: CELL CULTURE COMPOSITIONS WITH ANTIOXIDANTS AND METHODS
 FOR POLYPEPTIDE PRODUCTION
 INVENTOR(S): VIJAYASANKARAN, Natarajan, South San Francisco, CA,
 UNITED STATES
 MEIER, Steven J., South San Francisco, CA, UNITED
 STATES
 VARMA, Sharat, South San Francisco, CA, UNITED STATES
 YANG, Yi, South San Francisco, CA, UNITED STATES
 PATENT ASSIGNEE(S): GENENTECH, INC., South San Francisco, CA, UNITED STATES
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140314779	A1	20141023
	US 10017732	B2	20180710
APPLICATION INFO.:	US 2014-14211416	A1	20140314 (14)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61799602	20130315 (61)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	66	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Page(s)	
LINE COUNT:	3940	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cell culture media comprising antioxidants are provided herein as are

methods of using the media for cell culturing and polypeptide production from cells. Compositions comprising polypeptides, such as therapeutic polypeptides, produced by the methods herein are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 10 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2014:291227 USPATFULL Full-text
TITLE: Process for the Production of Fine Chemicals
INVENTOR(S): Plesch, Gunnar, Potsdam, GERMANY, FEDERAL REPUBLIC OF
Blau, Astrid, Stahnsdorf, GERMANY, FEDERAL REPUBLIC OF
Herold, Michael Manfred, Berlin, GERMANY, FEDERAL
REPUBLIC OF
Kamlage, Beate, Berlin, GERMANY, FEDERAL REPUBLIC OF
Wendel, Birgit, Berlin, GERMANY, FEDERAL REPUBLIC OF
Puzio, Piotr, Mariakerke (Gent), BELGIUM
Henkes, Stefan, Potsdam, GERMANY, FEDERAL REPUBLIC OF
Haake, Volker, Berlin, GERMANY, FEDERAL REPUBLIC OF
Van Camp, Wim, Sint-Denijs-Westrem, BELGIUM
Fahnenstich, Holger, Berlin, GERMANY, FEDERAL REPUBLIC
OF
McKersie, Bryan, Raleigh, NC, UNITED STATES
Bruce, Wesley, Raleigh, NC, UNITED STATES
Christiansen, Nicole, Berlin, GERMANY, FEDERAL REPUBLIC
OF
PATENT ASSIGNEE(S): BASF Plant Science Company GmbH, Ludwigshafen, GERMANY,
FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20140259212	A1	20140911	
APPLICATION INFO.:	US 2012-13510783	A1	20101118	(13)
	WO 2010-EP6988		20101118	
			20120518	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2009-14472	20091118
	EP 2009-176396	20091118
	EP 2009-181052	20091222
	EP 2010-186930	20101008
	EP 2010-188863	20101026
	EP 2010-189169	20101028
	EP 2010-189358	20101029
	EP 2010-189943	20101104
	EP 2010-190115	20101105
	EP 2010-190348	20101108
	EP 2010-190441	20101109
	EP 2010-190649	20101110
	EP 2010-190780	20101111
	EP 2010-190795	20101111
	EP 2010-190934	20101112
	EP 2010-190974	20101112
	EP 2010-191021	20101112
	EP 2010-191126	20101115
	EP 2010-191238	20101115
	EP 2010-191282	20101116

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1-23
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 672727

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a process for the production of a fine chemical in a non-human organism, like a microorganism, a plant cell, a plant, a plant tissue or in one or more parts thereof. The invention furthermore relates to nucleic acid molecules, polypeptides, nucleic acid constructs, expression cassettes, vectors, antibodies, host cells, plant tissue, propagation material, harvested material, plants, microorganisms as well as agricultural compositions and to their use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2021 ACS on STN

ACCESSION NUMBER: 2014:376253 CAPLUS Full-text

TITLE: Iron mediated tryptophan oxidation and vitamin B12 carryover caused a brown color formation of protein drug substance manufactured in CHO cells using chemically defined media

AUTHOR(S): Xu, Jianlin; Jin, Mi; Song, Hangtian; Huang, Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger, Kirby; Lewen, Nancy S.; Tao, Li; Li, Zheng Jian

CORPORATE SOURCE: 1Biologics Process Development, Bristol-Myers Squibb Company, USA

SOURCE: Abstracts of Papers, 247th ACS National Meeting & Exposition, Dallas, TX, United States, March 16-20, 2014 (2014), BIOT-385. American Chemical Society: Washington, D. C.

CODEN: 69SHSU

DOCUMENT TYPE: Conference; Meeting Abstract; (online computer file)

LANGUAGE: English

AB Drug substance (DS) color is an important quality attribute for release, stability and comparability studies of therapeutic proteins. With the increase of DS concns. and biologics pipelines made in chem. defined media, atypical DS color other than colorless or pale yellow has been recently reported in the biopharmaceutical industry. This presentation reports an investigative approach to elucidate the root cause of a brown colored drug substance obsd. in manufg. using CHO cells. Although anal. characterization data indicated that the brown color DS had no major quality issue, it is necessary to find the root cause and reduce DS color to ease placebo design for clin. use. It was demonstrated that the brown color was caused by the chem. defined medium contg. high levels of iron, vitamin B12 (VB12), and copper regardless of cell lines. Iron caused tryptophan oxidn. in the protein to form N-formylkynurenine and kynurenine products, which likely contributed to a yellow DS color. A pink DS color was caused by the residual VB12 bound to DS. The brown color was the result of the combinatory effect of yellow and pink colors. In addn., high levels of iron in the basal medium promoted cell growth and protein titer, while high levels of VB12 had no impact on cell culture performance. Copper neither caused any DS color nor improved titer. Finally a modified basal medium was developed to produce a pale yellow DS in manufg. To our knowledge, this study advances knowledge of the mechanism of DS color formation and cell culture manufg. processes for therapeutic proteins.

L5 ANSWER 12 OF 15 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN

ACCESSION NUMBER: 2015:238056 BIOSIS Full-text

DOCUMENT NUMBER: PREV201500238056

TITLE: Iron mediated tryptophan oxidation and vitamin B12 carryover caused a brown color formation of protein drug substance manufactured in CHO cells using chemically defined media.

AUTHOR(S): Xu, Jianlin [Reprint Author]; Jin, Mi; Song, Hangtian; Huang, Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger, Kirby; Lewen, Nancy S.; Tao, Li; Li, Zheng Jian

CORPORATE SOURCE: Bristol Myers Squibb Co, Proc Dev 1Biol, New York, NY 10154 USA
jianlin.xu@bms.com

SOURCE: Abstracts of Papers American Chemical Society, (MAR 16 2014) Vol. 247, pp. 385-BIOT.
Meeting Info.: 247th National Spring Meeting of the American-Chemical-Society (ACS). Dallas, TX, USA. March 16 -20, 2014. Amer Chem Soc.

CODEN: ACSRAL. ISSN: 0065-7727.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 18 Mar 2015

Last Updated on STN: 18 Mar 2015

L5 ANSWER 13 OF 15 SCISEARCH COPYRIGHT (c) 2021 Clarivate Analytics on STN
 ACCESSION NUMBER: 2015:271312 SCISEARCH Full-text
 THE GENUINE ARTICLE: AZ8HD
 TITLE: Iron mediated tryptophan oxidation and vitamin B12
 carryover caused a brown color formation of protein drug
 substance manufactured in CHO cells using chemically
 defined media
 AUTHOR: Xu, Jianlin (Reprint); Jin, Mi; Song, Hangtian; Huang,
 Chao; Xu, Xuankuo; Tian, Jun; Qian, Nan-Xin; Steger,
 Kirby; Tao, Li; Li, Zheng Jian
 CORPORATE SOURCE: Bristol Myers Squibb Co, Proc Dev 1Biol, New York, NY
 10154 USA
 E-mail: jianlin.xu@bms.com
 AUTHOR: Lewen, Nancy S.
 CORPORATE SOURCE: Bristol Myers Squibb Co, Pharmaceut Dev, New York, NY
 10154 USA
 COUNTRY OF AUTHOR: USA
 SOURCE: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, (16
 MAR 2014) Vol. 247. MA 385-BIOT.
 ISSN: 0065-7727.
 PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036
 USA.
 DOCUMENT TYPE: Conference; Journal
 LANGUAGE: English
 REFERENCE COUNT: 0
 ENTRY DATE: Entered STN: 23 Feb 2015
 Last Updated on STN: 23 Feb 2015

L5 ANSWER 14 OF 15 USPATFULL on STN
 ACCESSION NUMBER: 2012:179338 USPATFULL Full-text
 TITLE: HCMV-related nucleic acids and microRNA
 INVENTOR(S): Bentwich, Itzhak, Kfar Daniel, ISRAEL
 PATENT ASSIGNEE(S): Rosetta Genomics, Inc., Rehovot, ISRAEL (non-U.S.
 corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 8207316	B1	20120626
APPLICATION INFO.:	US 2003-707003		20031030 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2003-604984, filed on 29 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2002-303778, filed on 26 Nov 2002, ABANDONED Continuation-in-part of Ser. No. US 2002-310188, filed on 5 Dec 2002, ABANDONED Continuation-in-part of Ser. No. US 2003-604945, filed on 27 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2003-604942, filed on 28 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2003-604943, filed on 28 Aug 2003, PENDING Continuation-in-part of Ser. No. US 2003-604944, filed on 28 Aug 2003, Pat. No. US 7217807 Continuation-in-part of Ser. No. US 2003-605838, filed on 30 Oct 2003, ABANDONED Continuation-in-part of Ser. No. US 2003-605840, filed on 30 Oct 2003, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-60457788	20030327 (60)
	US 2003-60441241	20030117 (60)
	US 2003-60411230	20030117 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Angell, J. E	
ASSISTANT EXAMINER:	Shin, Dana	
LEGAL REPRESENTATIVE:	Scott, Jr., Teddy, Polsinelli Shughart	
NUMBER OF CLAIMS:	4	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	26 Drawing Figure(s); 17 Drawing Page(s)	
LINE COUNT:	1069089	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	The present invention relates to a group of noel viral RNA regulatory	

genes, here identified as "viral genomic address messenger genes" or "VGAM genes", and as "Viral genomic record" or "VGR genes". VGAM genes selectively inhibit translation of known host target genes, and are believed to represent a pervasive viral attack mechanism. VGR genes encode an "operon"-like cluster of VGAM genes. VGAM and viral VGR genes may therefore be useful in diagnosing, preventing and treating viral disease. Several nucleic acid molecules are provided respectively encoding several VGAM genes, as are vectors and probes, both comprising the nucleic acid molecules, and methods and systems for detecting VGAM genes, and for counteracting their activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 15 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2004:25211 USPATFULL Full-text
TITLE: Combination of an allosteric carboxylic inhibitor of matrix metalloproteinase-13 with celecoxib or valdecoxib
INVENTOR(S): Roark, William Howard, Ann Arbor, MI, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040019053	A1	20040129
APPLICATION INFO.:	US 2003-619662	A1	20030715 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-60396903	20020717 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	WARNER-LAMBERT COMPANY, 2800 PLYMOUTH RD, ANN ARBOR, MI, 48105	
NUMBER OF CLAIMS:	9	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	No Drawings	
LINE COUNT:	8040	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a combination, comprising an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with celecoxib, or a pharmaceutically acceptable salt thereof, or valdecoxib, or a pharmaceutically acceptable salt thereof. This invention also provides a method of treating a disease that is responsive to inhibition of MMP-13 and cyclooxygenase-2, comprising administering to a patient suffering from such a disease the invention combination comprising an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with celecoxib, or a pharmaceutically acceptable salt thereof, or valdecoxib, or a pharmaceutically acceptable salt thereof. This invention also provides a pharmaceutical composition, comprising the invention combination comprising an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with celecoxib, or a pharmaceutically acceptable salt thereof, or valdecoxib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

The invention combination may also be further combined with other pharmaceutical agents depending on the disease being treated.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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(FILE 'HOME' ENTERED AT 20:39:57 ON 20 MAR 2021)
D SET
D CLUSTER

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS,

BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA, CIN, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGU, EMBASE, ESBIODBASE, FSTA, GENBANK, IFIALL, IMSRESEARCH, KOSMET, MEDLINE, NTIS, ...' ENTERED AT 20:40:12 ON 20 MAR 2021

SEA (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S)

122 FILE ADISCTI
6 FILE ADISINSIGHT
32 FILE AGRICOLA
48 FILE BIOSIS
105 FILE BIOTECHABS
105 FILE BIOTECHDS
42 FILE BIOTECHNO
31 FILE CABA
77 FILE CAPLUS
12 FILE CEABA
31 FILE DDFU
315 FILE DGENE
56 FILE DRUGU
61 FILE EMBASE
109 FILE ESBIODBASE
15 FILE FSTA
4 FILE GENBANK
885 FILE IFIALL
1 FILE IMSRESEARCH
1 FILE KOSMET
46 FILE MEDLINE
1 FILE NTIS
83 FILE PQSCITECH
45 FILE SCISEARCH
62 FILE TOXCENTER
1392 FILE USPATFULL
3 FILE USPATOLD
656 FILE USPAT2
11 FILE IPA

L1 QUE (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S)
(COLOR? OR COLOU?)

D RANK

FILE 'USPATFULL, IFIALL, USPAT2, ADISCTI, ESBIODBASE, BIOTECHDS, PQSCITECH, CAPLUS, TOXCENTER, EMBASE, DRUGU, BIOSIS, MEDLINE, SCISEARCH, BIOTECHNO, AGRICOLA, CABA' ENTERED AT 20:43:51 ON 20 MAR 2021

L2 3852 SEA (("CHO" (10A) CELL?) OR (CHINES? (3A) HAM?(3A) OVAR?)) (S)
(COLOR? OR COLOU?)

L3 331 SEA L2(S)(IRON? OR FERROU? OR FERRIC? OR ZINC? OR "ZN" OR COPPE? OR "CU" OR NICKE? OR "NI" OR CYSTEIN? OR "CYS" OR "ANTI-OXIDANT" OR ANTIOXIDAN? OR HYDROCORTISO?)

L4 15 SEA L3(S)((MEDIA? OR MEDIUM?) (20A)(DEFINE?))

L5 15 DUP REM L4 (0 DUPLICATES REMOVED)

D IBIB ABS L5 1-15

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FILE STNINDEX

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 18 Mar 2021 (20210318/PD)

FILE LAST UPDATED: 18 Mar 2021 (20210318/ED)

HIGHEST GRANTED PATENT NUMBER: US10952361

HIGHEST APPLICATION PUBLICATION NUMBER: US20210084802

CA INDEXING IS CURRENT THROUGH 14 Mar 2021 (20210314/UPCA)

New NUMERIC PROPERTY SEARCH available. See HELP NPS for more information.

PatentPak is now available in USPATFULL and USPAT2 to PatentPak licensors! See HELP PPAK in either database or the online STN news story for details.

To ensure comprehensive retrieval of US patent information, including US patent application information, search USPATFULL in combination with USPAT2.



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NOTICE OF ALLOWANCE AND FEE(S) DUE

151431 7590 06/28/2021
Kramer Levin Naftalis & Frankel LLP
1177 Avenue of the Americas
New York, NY 10036

EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 06/28/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/996,030	08/18/2020	Shawn Lawrence	070816-02250	3885

TITLE OF INVENTION: METHODS FOR PRODUCING AFLIBERCEPT IN CHEMICALLY DEFINED MEDIA HAVING REDUCED AFLIBERCEPT VARIANTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	09/28/2021

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 ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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.

151431 7590 06/28/2021
Kramer Levin Naftalis & Frankel LLP
1177 Avenue of the Americas
New York, NY 10036

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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

	(Typed or printed name)
	(Signature)
	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/996.030	08/18/2020	Shawn Lawrence	070816-02250	3885

TITLE OF INVENTION: METHODS FOR PRODUCING AFLIBERCEPT IN CHEMICALLY DEFINED MEDIA HAVING REDUCED AFLIBERCEPT VARIANTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	09/28/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAMIREZ, DELIA M	1652	435-071100

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

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

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/996,030	08/18/2020	Shawn Lawrence	070816-02250	3885
151431	7590	06/28/2021	EXAMINER	
Kramer Levin Naftalis & Frankel LLP			RAMIREZ, DELIA M	
1177 Avenue of the Americas			ART UNIT	
New York, NY 10036			PAPER NUMBER	
			1652	
DATE MAILED: 06/28/2021				

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

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

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.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B 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 30 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.

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. 16/996,030	Applicant(s) Lawrence et al.	
	Examiner DELIA M RAMIREZ	Art Unit 1652	AIA (FITF) Status Yes

-- 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 6/11/2021.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

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 9-21 and 30-32. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

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. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ 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).

6. ☐ 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)

1. ☐ Notice of References Cited (PTO-892) 2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>3/19/21</u> . 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☒ Interview Summary (PTO-413), Paper No./Mail Date. <u>attached</u> .	5. ☒ Examiner's Amendment/Comment 6. ☒ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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/DELIA M RAMIREZ/
Primary Examiner, Art Unit 1652

DETAILED ACTION

Status of the Application

Claims 9-21, 30-32 are pending.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Amendment of claims 9-10, 14-19, 21, 30, cancellation of claims 1-8, 22-29, and addition of claims 31-32 as submitted in a communication filed on 6/11/2021 are acknowledged.

In a telephone conversation with Mr. Jonathan Caplan on 6/16/2021, an agreement was reached to amend claims 10, 14, 16, 20, 31 to place the application in condition for allowance.

Linking claim 1 has been cancelled. However, claim 18 as amended is now a linking claim that links inventions I-V as set forth in the restriction requirement of 10/15/2020. In accordance with MPEP 809, in view of the allowance of linking claim 18, the previous restriction requirement among inventions I-V is hereby *withdrawn*.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 3/19/2021 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements has been considered by the examiner.

Examiner's Amendment

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

3. Authorization for this Examiner's amendment was given in a telephone interview with Mr. Jonathan Caplan on 6/16/2021.

4. Please replace claims 10, 14, 16, 20, 31 as follows:

10. The method of claim 18, wherein said harvest comprises one or more aflibercept variants, wherein said variants have at least one oxidized amino acid residue.

14. The method of claim 10, wherein said aflibercept variant comprises a polypeptide having an amino acid sequence selected from the group consisting of: SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71 and combinations thereof.

16. The method of claim 17, wherein the color of harvest is characterized in the CIE L*, a*, b* color space, where L* is about 70 to about 99, a* is about 0 and b* is about 20 or less than 20 when the concentration of aflibercept is 5.0 g/L.

20. The method of claim 19, wherein said anti-oxidants are taurine, hypotaurine, glycine, thiocetic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

31. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

- (a) providing a host cell genetically engineered to express aflibercept;
- (b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is about 0.4 μM and one or more of the following:
 - i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM ;

- ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM ;
 - iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM ;
 - iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and
 - v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
- (c) harvesting aflibercept produced by said host cell, wherein the color of said harvest is:
- a. no more yellow-brown than European Color Standard BY2;
 - b. no more yellow-brown than European Color Standard BY3;
 - c. no more yellow-brown than European Color Standard BY4;
 - d. no more yellow-brown than European Color Standard BY5;
 - e. between European Color Standard BY2 and BY3; or
 - f. between European Color Standard BY2 and BY4,
- wherein the aflibercept concentration is 5.0 g/L.

Reasons for Allowance

5. The following is an Examiner's statement of reasons for allowance. Although the prior art discloses a method to culture eukaryotic cells, including CHO cells, to produce recombinant proteins, including aflibercept, having amino acids which are less oxidized so that the color of the recombinant proteins is lighter, wherein said method requires a chemically defined culture media comprising specific compounds at certain concentration ranges (Vijayasankaran et al., US Publication No. 2013/0281355 published 10/24/2013; cited in prior Office actions), and discloses culturing eukaryotic host cells that

produce aflibercept, including CHO cells, in a chemically defined medium that comprises taurine (antioxidant) at the recited ranges to produce aflibercept, the Examiner has found no teaching or suggestion in the prior art directed to a method for producing aflibercept by culturing a host cell that expresses aflibercept in a chemically defined medium (CDM) that comprises a cumulative concentration of nickel of about 0.4 μM or less than or equal to 0.4 μM and further comprises (i) a cumulative concentration of iron in said CDM that is less than or equal to 55.0 μM , (ii) a cumulative concentration of copper in said CDM that is less than or equal to 0.8 μM , (iii) a cumulative concentration of zinc in said CDM that is less than or equal to 56.0 μM , (iv) a cumulative concentration of cysteine in said CDM that is less than or equal to 10.0 mM, and/or (v) one or more antioxidants, wherein the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant. Therefore, claims 9-21, 30-32, directed to a method for producing aflibercept by (a) culturing a host cell that expresses aflibercept in a chemically defined medium (CDM) that comprises a cumulative concentration of nickel of about 0.4 μM or less than or equal to 0.4 μM and further comprises (i) a cumulative concentration of iron in said CDM that is less than or equal to 55.0 μM , (ii) a cumulative concentration of copper in said CDM that is less than or equal to 0.8 μM , (iii) a cumulative concentration of zinc in said CDM that is less than or equal to 56.0 μM , (iv) a cumulative concentration of cysteine in said CDM that is less than or equal to 10.0 mM, and/or (v) one or more antioxidants, wherein the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant, and (b) harvesting said aflibercept produced by said host cell, are allowable over the prior art of record.

Conclusion

6. Claims 9-21, 30-32 are allowed.
7. 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."

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DELIA M RAMIREZ, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (408) 918-7584. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/DELIA M RAMIREZ/
Primary Examiner, Art Unit 1652

DR
June 17, 2021

<i>Examiner-Initiated Interview Summary</i>	Application No. 16/996,030	Applicant(s) Lawrence et al.		
	Examiner DELIA M RAMIREZ	Art Unit 1652	AIA (First Inventor to File) Status Yes	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
DELIA M RAMIREZ	Primary Examiner	Telephonic
Jonathan Caplan	Attorney of Record	

Date of Interview: 16 June 2021

Issues Discussed:

Proposed Amendment(s)

The examiner contacted Mr. Caplan to propose an examiner's amendment to place the application in condition for allowance. Specifically, the examiner proposed (i) deleting the term "clarified" in claim 10 due to lack of antecedent basis, (ii) changing the term "claim 18" with "claim 10" in claim 14 due to lack of antecedent basis for variants in claim 18, (iii) changing the term "claim 18" with "claim 17" in claim 16 to overcome a previous indefiniteness rejection, (iv) changing in claim 20 the term "anti-oxidant is taurine" with "anti-oxidants are taurine" to be consistent with the language of claim 18, and (v) deleting in claim 31 the term "less than or equal to 0.4 micromolar" to avoid duplication with claim 17. Mr. Caplan agreed to the proposed amendments.

/DELIA M RAMIREZ/ Primary Examiner, Art Unit 1652	
Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04 Please further see: MPEP 713.04 Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b) 37 CFR § 1.2 Business to be transacted in writing	

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

<i>Index of Claims</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	10/10/2020	11/22/2020	03/20/2021	06/19/2021					
	1	÷	✓	✓	-					
	2	÷	✓	✓	-					
	3	÷	✓	✓	-					
	4	÷	✓	✓	-					
	5	÷	✓	✓	-					
	6	÷	✓	✓	-					
	7	÷	✓	✓	-					
	8	÷	✓	✓	-					
6	9	÷	✓	✓	=					
7	10	÷	✓	✓	=					
8	11	÷	✓	✓	=					
9	12	÷	✓	✓	=					
10	13	÷	✓	✓	=					
11	14	÷	✓	✓	=					
12	15	÷	✓	✓	=					
14	16	÷	✓	✓	=					
13	17	÷	✓	✓	=					
1	18	÷	✓	✓	=					
2	19	÷	✓	✓	=					
3	20	÷	✓	✓	=					
4	21	÷	✓	✓	=					
	22	÷	✓	✓	-					
	23	÷	✓	✓	-					
	24	÷	✓	✓	-					
	25	÷	✓	✓	-					
	26	÷	✓	✓	-					
	27	÷	✓	✓	-					
	28	÷	✓	✓	-					
	29	÷	✓	✓	-					
5	30	÷	✓	✓	=					
15	31				=					
16	32				=					

<i>Search Notes</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

CPC - Searched*		
Symbol	Date	Examiner
C07K14/71; C12P21/02; C07K2319/30	11/27/2020	DR

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STN- index bioscience medicine - see search history and entire transcript	11/27/2020	DR
WEST- USPT, PGPB, DWPI, EPAB, JPAB- see search history	11/27/2020	DR
PALM- inventor search-Shawn Lawrence,Amy Johnson, Meghan Casey, Jaimie Mastrogiacomo, Shunhai Wang, Ning Li	11/27/2020	DR
parent cases considered-63/065,012	11/27/2020	DR
STN/WEST-updated search of 11/27/2020	03/20/2021	DR

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<i>Search Notes</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
WEST	USPT, PGPB-double patenting and interference-see search history	06/19/2021	DR
sequence search	SEQ ID NO:17-23,62-71-protein databases-commercial & interference	06/19/2021	DR
	C07K14/71; C12P21/02; C07K2319/30	06/19/2021	DR

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<i>Issue Classification</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

CPC						
Symbol					Type	Version
C07K	/	14	/	71	F	2013-01-01
C12P	/	21	/	02	I	2013-01-01
C07K	/	2319	/	30	A	2013-01-01

CPC Combination Sets							
Symbol				Type	Set	Ranking	Version
	/		/				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	16	
/DELIA M RAMIREZ/	19 June 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

<i>Issue Classification</i> 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

INTERNATIONAL CLASSIFICATION			
CLAIMED			
C12P21/02	/	21	/ 02
NON-CLAIMED			
C07K14/71	/	14	/ 71

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	16	
/DELIA M RAMIREZ/ Primary Examiner, Art Unit 1652	19 June 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification 	Application/Control No. 16/996,030	Applicant(s)/Patent Under Reexamination Lawrence et al.
	Examiner DELIA M RAMIREZ	Art Unit 1652

☐ Claims renumbered in the same order as presented by applicant
 ☐ CPA
 ☐ T.D.
 ☐ R.1.47

CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
6	9	1	18												
7	10	2	19												
8	11	3	20												
9	12	4	21												
10	13	5	30												
11	14	15	31												
12	15	16	32												
14	16														
13	17														

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	16	
/DELIA M RAMIREZ/ Primary Examiner, Art Unit 1652	19 June 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		16996030	
	Filing Date		2020-08-18	
	First Named Inventor	Shawn Lawrence		
	Art Unit	1652		
	Examiner Name	Delia M. Ramirez		
	Attorney Docket Number	070816-02250		

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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/D.R/	1	WO2015/058369	WO	A1	2015-04-30	Sanofi China Invest Co. Ltd.		☐
/D.R/	2	WO2013/028330	WO	A2	2013-02-28	Emd Millipore Corp.		☐

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/DELIA M RAMIREZ/

06/19/2021

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	16996030
Filing Date	2020-08-18
First Named Inventor	Shawn Lawrence
Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	070816-02250

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
/D.R./	1	YAN AN ET AL., "A new tool for monoclonal antibody analysis: Application of IdeS proteolysis in IgG domain-specific characterization," MABS, vol. 6, no. 4, 7 April 2014 (2014-04-07), pages 879-893	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/DELIA M RAMIREZ/	Date Considered	06/19/2021
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.



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BIB DATA SHEET

CONFIRMATION NO. 3885

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/996,030	08/18/2020	435	1652	070816-02250
RULE				
APPLICANTS Regeneron Pharmaceuticals, Inc., Tarrytown, NY				
INVENTORS Shawn Lawrence, Nyack, NY; Amy Johnson, Briarcliff Manor, NY; Meghan Casey, Ringwood, NJ; Jaimie Mastrogiacono, White Plains, NY; Shunhai Wang, Ossining, NY; Ning Li, New Canaan, CT;				
DR 6/17/2021				
** CONTINUING DATA ***** This appln claims benefit of 63/065,012 08/13/2020 and claims benefit of 62/944,635 12/06/2019				
** FOREIGN APPLICATIONS *****				
** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 09/17/2020				
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged <u>/DELIA M RAMIREZ/</u> Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY NY	SHEETS DRAWINGS 60	TOTAL CLAIMS 30
INDEPENDENT CLAIMS 3				
ADDRESS Kramer Levin Naftalis & Frankel LLP 1177 Avenue of the Americas New York, NY 10036 UNITED STATES				
TITLE METHODS FOR PRODUCING AFLIBERCEPT IN CHEMICALLY DEFINED MEDIA HAVING REDUCED AFLIBERCEPT VARIANTS				
FILING FEE RECEIVED 4080	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	) Examiner: Ramirez, Delia M.
	)
Shawn Lawrence et al.	) Art Unit: 1652
	)
Application No: 16/996,030	) Confirmation No.: 3885
	)
Filed: August 18, 2020	) CERTIFICATE OF ELECTRONIC
	) FILING
For: METHODS FOR PRODUCING	) I hereby certify that this correspondence is
AFLIBERCEPT IN CHEMICALLY	) being submitted electronically via EFS Web
DEFINED MEDIA HAVING REDUCED	) on the date shown below.
AFLIBERCEPT VARIANTS	)
	)
	) <u>/Diane Torniali/ June 11, 2021</u>
	) Diane Torniali Date
	)
	)

RESPONSE AFTER FINAL REJECTION

E-Filed via EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

OK TO ENTER: /D.R/
06/19/2021

Commissioner:

In response to the Final Office Action dated March 24, 2021, Applicant respectfully requests the Examiner to consider the following remarks. This response is being submitted within the initial term for response.

Amendments to the Claims begin on page 2 of this document.

Remarks begin on page 7 of this document.

WEST Search History

DATE: Saturday, June 19, 2021

Hide?	<u>Set</u> <u>Name</u>	<u>Query</u>	<u>Hit</u> <u>Count</u>
		<i>DB=PGPB,USPT; PLUR=YES; OP=OR</i>	
☐	L19	L18 and (regeneron.asn. or regeneron.aanm. or (Lawrence or Johnson or casey or (wang near3 shunhai) or (li near3 ning) or mastrogiacono).in.)	0
☐	L18	L7 and ("aflibercept" or "vegf-trap" or "vegf trap" or "vegf trap eye" or "vegftap eye")	34
☐	L17	L16 and ("aflibercept" or "vegf-trap" or "vegf trap" or "vegf trap eye" or "vegftap eye")	0
☐	L16	(l1 or l8 or l14) and (regeneron.asn. or regeneron.aanm. or (Lawrence or Johnson or casey or (wang near3 shunhai) or (li near3 ning) or mastrogiacono).in.)	23
☐	L15	L14 and ("aflibercept" or "vegf-trap" or "vegf trap" or "vegf trap eye" or "vegftap eye")	0
☐	L14	L12 and l8	39
☐	L13	L12 and l1	0
☐	L12	(C07K14/71 or C12P21/02 or C07K2319/30).cpc.	18283
☐	L11	L1 and l7	0
☐	L10	L1 and ("aflibercept" or "vegf-trap" or "vegf trap" or "vegf trap eye" or "vegftap eye")	0
☐	L9	L8 and ("aflibercept" or "vegf-trap" or "vegf trap" or "vegf trap eye" or "vegftap eye")	3
☐	L8	L7 and (nickel\$4 or "ni")	591
☐	L7	("cho" or (chines\$4 adj3 ham\$4 adj3 ovar\$4)) same (color\$3 or colou\$4)	2285
☐	L1	(nickel\$4 or "ni") same ("cho" or (chine\$4 adj3 ham\$4 adj3 ovar\$4)) same ((chemi\$5 adj3 defin\$4 adj3 medi\$4) or "cdm")	50

END OF SEARCH HISTORY

ALLOWED CLAIMS:

- 1-8. (Cancelled)
9. (Currently Amended) The method of claim 18, wherein said host cell is selected from the group consisting of CHO, NS0, Sp2/0, embryonic kidney cell and BHK.
10. (Currently Amended) The method of claim 18, wherein said harvest comprises one or more aflibercept variants, wherein said variants have at least one oxidized amino acid residue.
11. (Original) The method of claim 10, wherein said oxidized amino acid residue is selected from the group consisting of methionine, tryptophan, histidine, phenylalanine, tyrosine and a combination thereof.
12. (Original) The method of claim 11, wherein said oxidized amino acid residue is histidine.
13. (Original) The method of claim 11, wherein said oxidized amino acid residue is tryptophan.
14. (Currently Amended) The method of claim 10, wherein said aflibercept variant comprises a polypeptide having an amino acid sequence selected from the group consisting of: SEQ ID NO.: 17, SEQ ID NO.: 18, SEQ ID NO.: 19, SEQ ID NO.: 20, SEQ ID NO.: 21, SEQ ID NO.: 22, SEQ ID NO.: 23, SEQ ID NO.: 62, SEQ ID NO.: 63, SEQ ID NO.: 64, SEQ ID NO.: 65, SEQ ID NO.: 66, SEQ ID NO.: 67, SEQ ID NO.: 68, SEQ ID NO.: 69, SEQ ID NO.: 70, SEQ ID NO.: 71 and combinations thereof.
15. (Currently Amended) The method of claim 18, wherein said anti-oxidants are taurine, hypotaurine, glycine, thiocetic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.
16. (Currently Amended) The method of claim 17, wherein the color of harvest is characterized in the CIE L*, a*, b* color space, where L* is about 70 to about 99, a* is about 0 and b* is about 20 or less than 20 when the concentration of aflibercept is 5.0 g/L.
17. (Currently Amended) The method of claim 18, wherein the harvest has a color that is:
 - a. no more yellow-brown than European Color Standard BY2;
 - b. no more yellow-brown than European Color Standard BY3;

- c. no more yellow-brown than European Color Standard BY4;
 - d. no more yellow-brown than European Color Standard BY5;
 - e. between European Color Standard BY2 and BY3; or
 - f. between European Color Standard BY2 and BY4, and
- wherein the aflibercept concentration in the harvest is 5.0 g/L.

18. (Currently amended) A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

- (a) providing a host cell genetically engineered to express aflibercept;
- (b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μ M or about 0.4 μ M and one or more of the following:
 - i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μ M;
 - ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μ M;
 - iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μ M;
 - iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and
 - v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
- (c) harvesting aflibercept produced by said host cell.

19. (Currently Amended) The method of claim 18, wherein said harvest has a color no more yellow-brown than European Color Standard BY2, wherein the aflibercept concentration is 5.0 g/L.

..

20. (Original) The method of claim 19, wherein said anti-oxidant are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

21. (Currently Amended) The method of claim 19, wherein said cumulative concentration of an anti-oxidant in said CDM is about 0.001 mM to about 10.0 mM for any single anti-oxidant and the cumulative concentration of all anti-oxidants is about 30.0 mM or less than 30.0 mM.

22-29. (Cancelled)

30. (Currently Amended) The method of claim 18, wherein aflibercept titer, viable cell concentration, viability, ammonia or osmolality is substantially unchanged.

31. (New) A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

- (a) providing a host cell genetically engineered to express aflibercept;
- (b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept, wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μ M or about 0.4 μ M and one or more of the following:
 - i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μ M;
 - ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μ M;
 - iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μ M;
 - iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and
 - v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
- (c) harvesting aflibercept produced by said host cell, wherein the color of said

harvest is:

- a. no more yellow-brown than European Color Standard BY2;
- b. no more yellow-brown than European Color Standard BY3;
- c. no more yellow-brown than European Color Standard BY4;
- d. no more yellow-brown than European Color Standard BY5;

- e. between European Color Standard BY2 and BY3; and/or
- f. between European Color Standard BY2 and BY4, wherein the aflibercept concentration is 5.0 g/L.

32. (New) A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

- (a) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following:
 - i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM ;
 - ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM ;
 - iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM ;
 - iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and
 - v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
- (b) harvesting aflibercept produced by said host cell.

Dated: June 11, 2021

TRADUCCION AL ESPAÑOL DE LA NOTIFICACIÓN DE CONCESIÓN

ACCIÓN DETALLADA

Estado de la Solicitud

Las reivindicaciones 9-21, 30-32 están pendientes.

La presente solicitud, presentada en o después del 16 de marzo de 2013, está siendo examinada por el primer inventor que presentó las disposiciones de la AIA.

Se reconocen las enmiendas de las reivindicaciones 9-10, 14-19, 21, 30, la cancelación de las reivindicaciones 1-8, 22-29 y la adición de las reivindicaciones 31-32 tal como se presentaron en una comunicación presentada el 11/06/2021.

En una conversación telefónica con el Sr. Jonathan Caplan el 16/06/2021, se llegó a un acuerdo para enmendar las reivindicaciones 10, 14, 16, 20, 31 para colocar la solicitud en condición de otorgamiento.

Se canceló la reivindicación de vinculación 1. Sin embargo, la reivindicación 18 enmendada es ahora una reivindicación vinculante que vincula las invenciones I-V tal como se establece en el requerimiento de restricción del 15/10/2020. De acuerdo con MPEP 809, en vista de la concesión de la vinculación de la reivindicación 18, se *retira* el requerimiento de restricción anterior entre las invenciones I-V.

Declaración de Divulgación de Información

1. Se reconoce la declaración de divulgación de información (IDS por sus siglas en inglés) presentada el 19/03/2021. La presentación cumple con las disposiciones de 37 CFR 1.97. En consecuencia, las declaraciones de divulgación de información han sido consideradas por el examinador.

Enmienda del examinador

2. La enmienda de un examinador al registro aparece a continuación. Si los cambios y/o adiciones son inaceptables para el solicitante, se puede presentar una enmienda según lo dispuesto en 37 CFR 1.312. Para garantizar la consideración de dicha enmienda, DEBE presentarse antes del pago de la tasa de emisión.

3. La autorización para esta enmienda del Examinador se dio en una entrevista telefónica con el Sr. Jonathan Caplan el 16/06/2021.

4. Por favor, reemplace las reivindicaciones 10, 14, 16, 20, 31 de la siguiente manera:

10. El método de la reivindicación 18, en donde dicha cosecha comprende una o más variantes de aflibercept, en donde dichas variantes tienen al menos un residuo de aminoácido oxidado.

14. El método de la reivindicación 10, en donde dicha variante de aflibercept comprende un polipéptido que tiene una secuencia de aminoácidos seleccionada del grupo que consiste en: SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71 y combinaciones de los mismos.

16. El método de la reivindicación 17, en donde el color de la cosecha se caracteriza en el espacio de color CIE L*, a*, b*, en donde L* es aproximadamente 70 a aproximadamente 99, a* es aproximadamente 0 y b* es aproximadamente 20 o menos de 20 cuando la concentración de aflibercept es de 5,0 g/L.

20. El método de la reivindicación 19, en donde dichos antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatión, colina, hidrocortisona, vitamina C, vitamina E o combinaciones de los mismos.

31. Un método para producir aflibercept obtenido de una célula huésped cultivada en un medio químicamente definido (CDM por sus siglas en inglés), que comprende:

- (a) proporcionar una célula huésped genéticamente diseñada para expresar aflibercept;
- (b) cultivar dicha célula huésped en dicho CDM en condiciones adecuadas en las que dicha célula huésped expresa dicho aflibercept en donde la concentración acumulada de níquel en dicho CDM es de aproximadamente 0,4 μM y uno o más de los siguientes:

- i. la concentración acumulada de hierro en dicho CDM es inferior o igual a 55,0 μM ;
 - ii. la concentración acumulada de cobre en dicho CDM es menor o igual a 0,8 μM ;
 - iii. la concentración acumulada de zinc en dicho CDM es menor o igual a 56,0 μM ;
 - iv. la concentración acumulada de cisteína en dicho CDM es menor o igual a 10,0 mM; y
 - v. dicho CDM incluye antioxidantes en donde la concentración acumulada de un antioxidante es de aproximadamente 0,001 mM a aproximadamente 10,0 mM para cualquier antioxidante único;
- y
- (c) recolectar aflibercept producido por dicha célula huésped, en donde el color de dicha cosecha es:
- a. no más amarillo-marrón que el European Color Standard BY2;
 - b. no más amarillo-marrón que el European Color Standard BY3;
 - c. no más amarillo-marrón que el European Color Standard BY4;
 - d. no más amarillo-marrón que el European Color Standard BY5;
 - e. entre el European Color Standard BY2 y BY3; o
 - f. entre el European Color Standard BY2 y BY4,
- en donde la concentración de aflibercept es de 5,0 g/l.

Razones para el otorgamiento

5. La siguiente es la declaración de un Examinador de las razones para el otorgamiento. Aunque el estado de la técnica da a conocer un método para cultivar células eucariotas, incluidas las células CHO, para producir proteínas recombinantes, incluido el aflibercept, que tienen aminoácidos menos oxidados para que el color de las proteínas recombinantes sea más claro, en donde dicho método requiere un medio de cultivo químicamente definido que comprende compuestos específicos en ciertos intervalos de concentración

(Vijayasankaran et al., publicación de EE. UU. No. 2013/0281355 publicada el 24/10/2013; citado en acciones Oficiales previas), y divulga el cultivo de células huésped eucariotas que producen aflibercept, incluidas las células CHO, en un medio químicamente definido que comprende taurina (antioxidante) en los intervalos enumerados para producir aflibercept, el Examinador no ha encontrado ninguna enseñanza o sugerencia en el estado de la técnica dirigida a un método para producir aflibercept mediante el cultivo de una célula huésped que expresa aflibercept en un medio químicamente definido (CDM) que comprende una concentración acumulada de níquel de aproximadamente $0,4\ \mu\text{M}$ o menor o igual a $0,4\ \mu\text{M}$ y comprende además (i) una concentración acumulada de hierro en dicho CDM que es menor o igual a $55,0\ \mu\text{M}$, (ii) una concentración acumulada de cobre en dicho CDM que es menor o igual a $0,8\ \mu\text{M}$, (iii) una concentración acumulada de zinc en dicho CDM que es inferior o igual a $56,0\ \mu\text{M}$, (iv) una concentración acumulada de cisteína en dicho CDM que es inferior o igual a $10,0\ \text{mM}$, y/o (v) uno o más antioxidantes, en donde la concentración acumulada de un antioxidante es de aproximadamente $0,001\ \text{mM}$ a aproximadamente $10,0\ \text{mM}$ para cualquier antioxidante individual. Por lo tanto, las reivindicaciones 9-21, 30-32, dirigidas a un método para producir aflibercept mediante (a) cultivar una célula huésped que expresa aflibercept en un medio químicamente definido (CDM) que comprende una concentración acumulada de níquel de aproximadamente $0,4\ \mu\text{M}$ menor o menor que o igual a $0,4\ \mu\text{M}$ y además comprende (i) una concentración acumulada de hierro en dicho CDM que es menor o igual a $55,0\ \mu\text{M}$, (ii) una concentración acumulada de cobre en dicho CDM que es menor o igual a $0,8\ \mu\text{M}$, (iii) una concentración acumulada de zinc en dicho CDM que es menor o igual a $56,0\ \mu\text{M}$, (iv) una concentración acumulada de cisteína en dicho CDM que es menor o igual a $10,0\ \text{mM}$, y/o (v) una o más antioxidantes, en donde la concentración acumulada de un antioxidante es de aproximadamente $0,001\ \text{mM}$ a aproximadamente $10,0\ \text{mM}$ para cualquier antioxidante único, y (b) recolectar dicho aflibercept producido por dicha célula huésped, están permitidos en el estado de la técnica registrado.

Conclusión

6. Se otorgan las reivindicaciones 9-21, 30-32.
7. Cualquier observación que el solicitante considere necesaria deberá presentarse como máximo antes del pago de la tasa de emisión y, para evitar retrasos en la tramitación, deberán acompañar preferentemente a

la tasa de emisión. Dichas presentaciones deben estar claramente etiquetados como "Comentarios sobre la Declaración de Razones para el Otorgamiento".

REIVINDICACIONES

1 a 8. (Canceladas)

9. (Actualmente modificada) El método de conformidad con la reivindicación 18, caracterizado porque tal célula hospedera se selecciona a partir del grupo que consiste de CHO, NS0, Sp2/0, células renales embrionicas y BHK.

10. (Actualmente modificada) El método de conformidad con la reivindicación 18, caracterizado porque tal recolección comprende una o más variantes de aflibercept, en donde tales variantes tienen al menos un residuo de aminoácido oxidado.

11. (Original) El método de conformidad con la reivindicación 10, caracterizado porque tal residuo de aminoácido oxidado se selecciona a partir del grupo que consiste de metionina, triptofano, histidina, fenilalanina, tirosina y una combinación de las mismas.

12. (Original) El método de conformidad con la reivindicación 11, caracterizado porque tal residuo de aminoácido oxidado es histidina.

13. (Original) El método de conformidad con la reivindicación 11, caracterizado porque tal residuo de aminoácido oxidado es triptofano.

14. (Actualmente modificada) El método de conformidad con la reivindicación 10, caracterizado porque tal variante de aflibercept comprende un polipéptido que tiene una secuencia de aminoácido seleccionada a partir del grupo que consiste de: SEQ ID NO.: 17, SEQ ID NO.: 18, SEQ ID NO.: 19, SEQ ID NO.: 20, SEQ ID NO.: 21, SEQ ID NO.: 22, SEQ ID NO.: 23, SEQ ID NO.: 62, SEQ ID NO.: 63, SEQ ID NO.: 64, SEQ ID NO.: 65, SEQ ID NO.: 66, SEQ ID NO.: 67, SEQ ID NO.: 68, SEQ ID NO.: 69, SEQ ID NO.: 70, SEQ ID NO.: 71 y combinaciones de las mismas.

15. (Actualmente modificada) El método de conformidad con la reivindicación 18, caracterizado porque tales antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatona, colina, hidroclotisona, Vitamina C, Vitamina E o combinaciones de los mismos.

16. (Actualmente modificada) El método de conformidad con la reivindicación 17, caracterizado porque el color de la recolección es caracterizado en el espacio de color L*, a*, b*, de CIE, donde L* es aproximadamente 70 hasta aproximadamente 99, a* es aproximadamente 0 y b* es aproximadamente 20 o menos de 20 cuando la concentración de aflibercept es 5,0 g/L.

17. (Actualmente modificada) El método de conformidad con la reivindicación 18, caracterizado porque la recolección tiene un color que es:

a. no más amarillo-marrón que el Estándar Europeo de Color BY2;

- b. no más amarillo-marrón que el Estándar Europeo de Color BY3;
- c. no más amarillo-marrón que el Estándar Europeo de Color BY4;
- d. no más amarillo-marrón que el Estándar Europeo de Color BY5;
- e. entre el Estándar Europeo de Color BY2 y BY3; o
- f. entre el Estándar Europeo de Color BY2 y BY4, y

en donde la concentración de aflibercept en la recolección es 5,0 g/L.

18. (Actualmente modificada) Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende:

(a) proporcionar una célula hospedera diseñada por ingeniería genética para expresar aflibercept;

(b) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 μM o aproximadamente 0,4 μM y uno o más de los siguientes;

- i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 μM ;
- ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 μM ;
- iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 μM ;
- iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM;

y

v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM a aproximadamente 10,0 mM para cualquier antioxidante único; y

(c) recolectar el aflibercept producido por tal célula hospedera.

19. (Actualmente modificada) El método de conformidad con la reivindicación 18, caracterizado porque tal recolección tiene un color no más amarillo-marrón que el Estándar Europeo de Color BY2, en donde la concentración de aflibercept es 5,0 g/l.

20. (Original) El método de conformidad con la reivindicación 19, caracterizado porque tales antioxidantes son taurina, hipotaurina, glicina, ácido tióctico, glutatión, colina, hidrocloruro, Vitamina C, Vitamina E o combinaciones de los mismos.

21. (Actualmente modificada) El método de conformidad con la reivindicación 19, caracterizado porque tal concentración acumulativa de un antioxidante en tal CDM es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para cualquier antioxidante único y la concentración

acumulativa de todos los antioxidantes es aproximadamente 30,0 mM o menos de 30,0 mM.

22 -29. (Canceladas)

30. (Actualmente modificada) El método de conformidad con la reivindicación 18, caracterizado porque el titulador de aflibercept, concentración celular viable, viabilidad, amoníaco u osmolalidad está sustancialmente sin cambio.

31. (Nueva) Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende:

(a) proporcionar una célula hospedera diseñada por ingeniería genética para expresar aflibercept;

(b) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a 0,4 μ M o aproximadamente 0,4 μ M y uno o más de los siguientes;

i. la concentración acumulativa de hierro en tal CDM es menor que o igual a 55,0 μ M;

ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a 0,8 μ M;

iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a 56,0 μ M;

iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a 10,0 mM;

y
v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente 0,001 mM hasta aproximadamente 10,0 mM para cualquier antioxidante único; y

(c) recolectar el aflibercept producido por tal célula hospedera, en donde el color de tal recolección es

a. no más amarillo-marrón que el Estándar Europeo de Color BY2;

b. no más amarillo-marrón que el Estándar Europeo de Color BY3;

c. no más amarillo-marrón que el Estándar Europeo de Color BY4;

d. no más amarillo-marrón que el Estándar Europeo de Color BY5;

e. entre el Estándar Europeo de Color BY2 y BY3; y/o

f. entre el Estándar Europeo de Color BY2 y BY4,

en donde la concentración de aflibercept es 5,0 g/L.

32. (Nueva) Un método para producir aflibercept recolectado a partir de una célula hospedera cultivada en un medio químicamente definido (CDM), caracterizado porque comprende:

(a) cultivar tal célula hospedera en tal CDM bajo condiciones adecuadas en las cuales

tal célula hospedera expresa tal aflibercept, en donde la concentración acumulativa de níquel en tal CDM es menor que o igual a $0,4\ \mu\text{M}$ o aproximadamente $0,4\ \mu\text{M}$ y uno o más de los siguientes;

- i. la concentración acumulativa de hierro en tal CDM es menor que o igual a $55,0\ \mu\text{M}$;
- ii. la concentración acumulativa de cobre en tal CDM es menor que o igual a $0,8\ \mu\text{M}$;
- iii. la concentración acumulativa de zinc en tal CDM es menor que o igual a $56,0\ \mu\text{M}$;
- iv. la concentración acumulativa de cisteína en tal CDM es menor que o igual a $10,0\ \text{mM}$;

y

v. tal CDM incluye antioxidantes, donde la concentración acumulativa de un antioxidante es aproximadamente $0,001\ \text{mM}$ hasta aproximadamente $10,0\ \text{mM}$ para cualquier antioxidante único; y

(b) recolectar el aflibercept producido por tal célula hospedera.