UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TRUTEK CORP.
Petitioner

v.

The REGENTS of the UNIVERSITY OF MICHIGAN
Patent Owner

U.S. Patent No. 10,138,279

Case IPR2022-00674

PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. § 312 AND 37 C.F.R. § 42.104

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TABLE OF AUTHORITIES

Cases:

Statutes and Other Authorities:

35 U.S.C. §§ 102, 103, pre-AIA 103(a), 112, 112(d), 312
37 CFR §§ 42.10(b), 42.100(b), 42.103, 42.104, 42.104(a), 42.105(a), 42.6(e)

LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 10,138,279 issued on November 27, 2018 to Baker, Jr., *et.al.*, titled "Compositions and Methods for *Bacillus Anthracis* Vaccination."
1002	Declaration of Dr. Edward Lemmo
1003	Declaration of Dennis O'Donnell
1004	U.S. Patent No. 5,961,970 issued on October 5, 1999 to Lowell, *et.al.*, titled "Submicron Emulsions as Vaccine Adjuvants."
1005	Yaghmur, et.al., *"Phase behavior of microemulsions based on food-grade nonionic surfactants: effect of polyols and short-chain alcohols*," Colloids & Surfaces, A. Physiochemical and Engineering Aspects, 209 (2002) 71-81.
1006	U.S. Patent No. 5,618,840 issued on April 8, 1997 to Wright, titled "Antibacterial Oil-in-Water Emulsions."
1007	Williamson, *et.al.*, " *Immunogenicity of Recombinant Protective Antigen and Efficacy Against Aerosol Challenge with Anthrax*," Infect. Immun. 2005 Sep. 73(9) 5978-5987.
1008	Baker, *et.al.*, "*Enhanced Systemic and Mucosal Immune Responses in Mice Immunized With Recombinant Bacillus anthracis Protective Antigen (rPA) Using a Novel Nanoemulsion Adjuvant*," J Allergy Clin Immunol, S292 Abstracts, No. 1064, (2004).
1009	Baker, *et.al.*, U.S. Patent Application Publication No. 2003/0194412 Al, published on October 16, 2003, titled, "Nanoemulsion Vaccines."

Petitioner Trutek Corp. ("Petitioner") requests *inter partes review* of claims 1-14 ("Challenged Claims") of U.S. Patent No. 10,138,279 B2 ("**'279 Patent**") (Exhibit 1001).

I. INTRODUCTION

The '279 Patent was issued to James R. Baker, Jr., Anna Bielinska, and Andrzej Myc on November 27, 2018, and it is assigned to the Regents of the University of Michigan. The '279 Patent is titled, "Compositions and Methods for *Bacillus Anthracis* Vaccination." The '279 Patent results from an allowance of claims in U.S. Patent Application No. 11/786,861, which was filed on April 13, 2007, and which in turn is the nonprovisional counterpart of U.S. Provisional Patent Application No. 60/791,759, Which was filed on April 13, 2006. The challenged claims (*i.e.*, claims 1-14) recite a nasally administered recombinant *B. anthracis* vaccine component contained within a nanoemulsion adjuvant. A nanoemulsion is a composition comprising an emulsion of oil, water, alcohol, and a surfactant in droplets having a diameter less than 1,000 nanometers. The patent has fourteen claims, of which two are independent. All claims are method claims, although they reference vaccine compositions. Independent claims 1 and 14 recite methods of administering the vaccines nasally. Claim 14 is stand alone, while claims 2-13 depend from claim 1.

The claims relate to stimulating an immune response to bacteria of the genus *B. anthracis* (*e.g.*, *Bacillus anthracis*) contained within the nanoemulsion adjuvant. The prior art teaches that nasally administered vaccines encapsulated

in nanoemulsion adjuvants yield greater efficacy than administering the vaccines intramuscularly without the nanoemulsion. Further, the prior art advocates utilization of *B. anthracis* vaccines in this way. Both the nanoemulsion component and the vaccine component, as well as their combination, can be derived from prior art. Several of the claims add limitations regarding efficacy, where the asserted limitations can be observed in the prior art. Other claims cite composition ranges of ingredients, presumably for optimization of the claimed composition, where those ranges can be derived using known and routine methods of experimentation.

Because the claimed compositions would have been obvious to combine, and because use in these compositions as prescribed would yield predictable results, the Challenged Claims are invalid.

II. MANDATORY NOTICES

A. Real Party-In-Interest

The real party-in-interest is Trutek Corp.

B. Related Matters

Although presently unrelated to this *inter partes* review (IPR), there is also a civil action in federal court in the Eastern District of Michigan, Trutek Corp. *v.* BlueWillow Biologics, Inc. ("BlueWillow"), Case No. 2:21-cv-10312, filed February 10, 2021. According to information and belief, at least one of the inventors listed in the '279 Patent is employed by BlueWillow. In addition, according to information and belief, the Patent Owner, *i.e.*, the Regents of the University of

Michigan, now does business with BlueWillow, a Delaware Corporation. The complaint alleges a single count of patent infringement of the claims of Trutek's US Patent No. 8,163,802 by BlueWillow's commercial product, NanoBio Protect. According to information and belief, by employing the technology of the '279 Patent, BlueWillow is developing an anthrax vaccine that also reads on Trutek's patent.

C. Counsel and Service Information

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Petitioner concurrently submits a Power of Attorney, 37 CFR § 42.10(b), and consents to electronic service directed to the following email address: uspto@patentsgroup.com.

III. PAYMENT OF FEES UNDER 37 CFR § 42.103

Payment of fees are submitted concurrently to the USPTO directly by the Petitioner *via* wire transfer.

IV. CERTIFICATION AND GROUNDS FOR STANDING

Petitioner certifies under 37 CFR § 42.104(a) that the '279 Patent is available for IPR and Petitioner is not barred or estopped from requesting IPR of the Challenged Claims on the grounds identified in this petition.

V. OVERVIEW OF CHALLENGE AND RELIEF REQUESTED

A. Prior Art References

- Exhibit 1004 (**Lowell**) - Lowell et.al., U.S. Patent No. 5,961,970 issued on October 5, 1999, titled, "Submicron Emulsions as Vaccine Adjuvants.". This reference is prior art under 35 U.S.C. § 102.
- Exhibit 1005 (**Yaghmur**) - Yaghmur, et.al., *"Phase behavior of microemulsions based on food-grade nonionic surfactants: effect of polyols and short-chain alcohols*," Colloids & Surfaces, A. Physiochemical and Engineering Aspects, 209 (2002) 71-81. This reference is prior art under 35 U.S.C. § 102.
- Exhibit 1006 (**Wright**) - Wright, U.S. Patent No. 5,618,840 issued on April 8, 1997, titled, "Antibacterial Oil-in-Water Emulsions." This reference is prior art under 35 U.S.C. § 102.
- Exhibit 1007 (**Williamson**) - Williamson, *et.al.*, " *Immunogenicity of Recombinant Protective Antigen and Efficacy Against Aerosol Challenge with Anthrax*," Infect. Immun. 2005 Sep. 73(9) 5978-5987. This reference is prior art under 35 U.S.C. § 102.
- Exhibit 1008 (**Baker S292 JACI**) - Baker, *et.al.*, "*Enhanced Systemic and Mucosal Immune Responses in Mice Immunized With Recombinant Bacillus anthracis Protective Antigen (rPA) Using a Novel Nanoemulsion Adjuvant*," J Allergy Clin Immunol, S292 Abstracts, No. 1064, (2004). This reference is prior art under 35 U.S.C. § 102.

- Exhibit 1009 (**Baker '412**) - Baker, *et.al.*, U.S. Patent Application Publication No. 2003/0194412 Al, published on October 16, 2003, titled, "Nanoemulsion Vaccines." This publication is based on U.S. Patent Application No. 10/162,970 filed on June 5, 2002, now U.S. Patent No. 7,314,324 B2 issued on January 1, 2008. This reference is prior art under 35 U.S.C. § 102.

B. Relief Requested

Petitioner requests IPR and cancellation of the Challenged Claims on the specific grounds set forth below, which are supported by the declarations of Dr. Edward Lemmo (Exhibit 1002) and Dennis O'Donnell (Exhibit 1003).

Ground	Claims	Proposed Statutory Rejection
1	1	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Lowell** (Exhibit 1004) in view of **Yaghmur** (Exhibit 1005), **Wright** (Exhibit 1006), and **Williamson** (Exhibit 1007), and further in view of **Baker S292 JACI** (Exhibit 1008).
2	1	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Baker '412** (Exhibit 1009) in view of **Williamson**, and further in view of **Baker S292 JACI**.
3	2	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Lowell** in view of **Yaghmur**, **Wright**, and **Williamson**, and further in view of **Baker S292 JACI**.
4	3	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Baker '412** in view of **Williamson**, and further in view of **Baker S292 JACI**.
5	4, 5, 12, 13	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Lowell** in view of **Yaghmur**, **Wright**, and **Williamson**, and further in view of **Baker S292 JACI**.

Ground	Claims	Proposed Statutory Rejection
6	6, 7	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Lowell** in view of **Yaghmur**, **Wright**, and **Williamson**, and further in view of **Baker S292 JACI**.
7	8	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Baker '412** in view of **Williamson**, and further in view of **Baker S292 JACI**.
8	9, 10, 11	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Lowell** in view of **Yaghmur**, **Wright**, and **Williamson**, and further in view of **Baker S292 JACI**.
9	9, 10, 11	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Baker '412** in view of **Williamson**, and further in view of **Baker S292 JACI**.
10	14	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Lowell** in view of **Yaghmur**, **Wright**, and **Williamson**, and further in view of **Baker S292 JACI**.
11	14	Obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over **Baker '412** in view of **Williamson**, and further in view of **Baker S292 JACI**.

VI. THE '279 PATENT

The '279 Patent (Exhibit 1001) issued on November 27, 2018 from U.S. Patent Application No. 11/786,861 (the '861 Application) filed on April 13, 2007 as the nonprovisional counterpart of U.S. Provisional Application 60/791,759 filed on April 13, 2006. The '861 Application published as U.S. 2015/0266933 on September 24, 2015.

A. Specification

The '279 Patent teaches methods for administering a vaccine to induce an immune response against anthrax (genus *Bacillus, e.g., B. anthracis*). The

vaccine functions to prevent symptoms of and mortality from anthrax. The disclosed vaccine composition has two components — a recombinant *Bacillus anthracis* protective antigen (rPA) component contained within a nanoemulsion adjuvant. In an exemplary embodiment, the vaccine is administered nasally. A nanoemulsion is an oil-in-water emulsion in the form of droplets having a diameter less than 1,000 nm. The nanoemulsion droplets normally contain a surfactant. Thus, the rPA (or vaccine component) is contained within each of the nanoemulsion droplets. Nanoemulsions are sometimes referred to as microemulsions or submicron emulsions. The terms are equivalent. Nanoemulsions represent excellent delivery systems for administration of vaccines, and increased efficacy may be expected from their use therein. The specification discloses experimental data of the efficacy of the nanoemulsion anthrax vaccines. The experiments were performed on animals. No data was presented for human subjects.

B. Claims

Petitioner challenges claims 1-14 under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a). Claims 1 and 14 are independent claims reciting methods of administering the nanoemulsion anthrax vaccine composition to subjects intranasally. Claims 2-13 depend directly from claim 1. The dependent claims either recite limitations to the composition, or they recite effects of the vaccine on inoculated subjects and comparing them to control subjects.

C. Prosecution History

The '279 Patent was issued based on the '861 Application filed at the USPTO on April 13, 2007. The initial filing comprised 32 claims. Claims 1, 18, and 30 were independent claims. Claims 1-17 were method claims; claims 18-29 were composition claims; and claims 30-32 were kit claims. The Examiner issued a total of eight office actions on the merits containing claim rejections over a period of five years.

The first office action issuing a restriction and requiring and election was mailed on October 13, 2011. The Examiner required an election either of claims 1-17 (the method claims) or claims 18-32 (the composition claims) for further prosecution. In response, the Applicant canceled claims 18-32, and added ten new method claims (*viz.*, claims 33-42). Claims 4-7 were also canceled.

Originally, claim 1 read as follows:

1. A method of inducing an immune response to *B. anthracis* in a subject comprising:
   a) providing a composition comprising a nanoemulsion and an immunogen, wherein said immunogen comprises recombinant protective antigen (rPA) of *B. anthracis;* and
   b) administering said composition to said subject under conditions such that said subject generates an immune response to said *B. anthracis.*

The first office action on the merits was mailed on February 17, 2012. In that action, the Examiner rejected all pending claims under 35 U.S.C. §§ 102, 103, and 112, and issued a provisional obviousness double patenting rejection. Most of the claims were rejected under 35 U.S.C. § 102 over Baker S292 JACI (Exhibit 1008). All of the claims were rejected under 35 U.S.C. §§ 102(e) and 103(a) for obviousness mostly over applications authored by Baker, *et.al.*, and

previously submitted to and published by the USPTO. In response, the Applicant amended claim 1 to read as follows:

1. (currently amended) A method of inducing an immune response to *Bacillus anthracis (B. anthracis)* in a subject comprising:
   a) providing an immunogenic composition comprising a nanoemulsion and an immunogen, wherein said immunogen comprises recombinant protective antigen (rPA) of *B. anthracis,* and wherein said nano emulsion comprises:
      1. oil·
      2. water;
      3. ethanol or glycerol;
      4. a polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
      5. cetylpyridinium chloride (CPC)**;** and
   b) administering said composition to said subject under conditions such that said subject generates an immune response to said *B. anthracis,* wherein the immune response comprises a rPA-specific humoral immune response and a rPA-specific cell mediated immune response.

In the next office action, the Examiner rejected all pending claims under 35 U.S.C. § 103(a) over Baker S292 JACI and an article by Hamouda. In response, the applicant amended claim 1, deleting the recitation of glycerol in element a(3).

Next, the Examiner rejected all claims under 35 U.S.C. § 103(a) over Baker S292 JACI and U.S. Patent No. 7,314,624 (Baker '624) titled, "Nanoemulsion Vaccines," issued to Baker, *et.al.*, on January 1, 2008. Technically, Baker '624 was not prior art, but the application upon which it is based was published as Baker '412 (Exhibit 1009) in 2002.

On December 1, 2015, in response to a final rejection under 35 U.S.C. § 103(a) over Baker S292 JACI and Baker '624, Applicants amended claim 1 once again.

1. (currently amended) A method of inducing an immune response to *Bacillus anthracis (B. anthracis)* in a subject comprising administering
   A) a nanoemulsion, wherein the nanoemulsion comprises
      1. oil;
      2. water;
      3. ethanol;
      4. polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
      5. cetylpyridinium chloride **(CPC);** and
   B) recombinant protective antigen (rPA) of *B. anthracis* to the subject to generate a *B. anthracis-specific* immune response, wherein the *B. anthracis-specific* immune response comprises generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that is at least 10 fold greater than the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline.

On January 26, 2017, the Applicant canceled 9 claims, leaving 17 pending claims remaining. On May 15, 2017, the Examiner once again rejected all pending claims under 35 U.S.C. § 103(a) over Baker S292 JACI, Baker '624, and Hanson, *et.al.*, J Clin Immunol. 2006 Feb; 13(2): 208-213. These rejections remained until the final rejection of January 16, 2018, Up until this point only claim 1 had been amended. On July 16, 2018, in response to the final rejection, Applicants amended claim 1 to its present content in the '279 Patent. Four dependent claims were amended, and some dependent claims were canceled. Independent claim 43 was newly added. Claim 43 (eventually renumbered to claim 14) did not contain the 10 fold antibody titer increase present in claim 1.

Finally, on September 21, 2018, the Examiner issued a Notice of Allowance of claims "1-2, 10-11, 13, 17, 33, 37-39 and 41-43 renumbered 1-14 respectively." Counting these allowed claims, we have only thirteen. Note that claim 8 was not allowed, but it was included in the '279 Patent as claim 3. In the

Notice of Allowability, the Examiner dwelt on the merits of claim 1, and its alleged ability to overcome the prior art. The apparent rationale for not delving into the dependent claims is that if an independent claim is allowable, all claims depending from it must also be allowable because each dependent claim incorporates all limitations of its base claim. However, the Examiner failed to explain any rationale for allowance of claim 14.

D. Person Having Ordinary Skill in the Art

In his Declaration (Exhibit 1002), Dr. Edward Lemmo opined on the nature of a person having ordinary skill in the art. "A person having ordinary skill in the art related to the '121 Patent would be familiar with the literature regarding the efficacy and safety of pharmaceutical products and biologics as well as recommended dosage ranges. Such a person should have an advanced degree in pharmaceutical chemistry and/or microbiology, and should have an understanding of vaccine technology."

VII. CLAIM CONSTRUCTION

Claims in an IPR are construed according to the standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). 37 C.F.R. §42.100(b).

A. Independent Claim 1

This is a method claim directed to inducing an immune response to *Bacillus anthracis* (*B. anthracis*), a source of infection commonly known as

anthrax. The preamble is limiting because it is specific to producing the immune response to the particular antigen. There are a number of limitations contained in claim 1.

1. Administration

The vaccine must be administered intranasally.

2. Composition of the Vaccine

a. Nanoemulsion Adjuvant

A nanoemulsion is an oil-in-water emulsion manifested as tiny droplets, each droplet having a diameter less than 1,000 nm. Nanoemulsions are also commonly known as micro emulsions and submicron emulsions. A nanoemulsion adjuvant is an efficient delivery system for foods, vitamins, and pharmaceuticals. They have been utilized since at least 1959.[1] Typically, in addition to oil and water, nanoemulsions also include alcohol and a surfactant. Nasal administration of a vaccine component in a nanoemulsion adjuvant should be expected to increase the delivery efficacy.

The nanoemulsion adjuvant of claim 1 comprises (1) oil; (2) water; (3) ethanol; (4) a polysorbate surfactant; and (cetylpyridinium chloride (CPC). The polysorbate surfactant is selected from a Markush group consisting of "polyoxyethylene sorbitan monooleate and polyoxyethylene monolaurate. CPC is a cationic surfactant.

[1] Schulman, *et.al., "Mechanism of Formation and Structure of Micro Emulsions By Electron Microscopy*," J. Phys. Chem. 1959, 63, 10, 1677-1680, Publication Date: October 1, 1959.

b. The Vaccine Component

The vaccine component is specified as the recombinant protective antigen (rPA) of *B. anthracis*.

3. Efficacy

"Generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that is at least 10 fold greater than the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline." As will be argued *infra*, this is a vague limitation.

B. Dependent Claim 2

Method claim 2 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. The claim recites that the composition contacts the nasal mucosal surface of the subject to which it is administered. This implies that nasal administration of the vaccine involves infusing the composition into the interior of the nostril.

C. Dependent Claim 3

Method claim 3 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. The claim recites that the immune response to *B. anthracis* is an immunoglobulin G (IgG) response to the rPA.

D. Dependent Claim 4

Method claim 4 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it imposes a limitation on the ingredients of the vaccine component of the composition. It specifies that the amount of rPA should be between 1 and 500 μg of rPA.

E. Dependent Claim 5

Method claim 5 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it imposes a limitation on the composition of the nanoemulsion vaccine such that the vaccine component ranges between 5% to 20% of the nanoemulsion solution.

F. Dependent Claim 6

Method claim 6 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it recites the efficacy of the nanoemulsion vaccine, which permits a subject to survive a lethal dose of *B. anthracis*.

G. Dependent Claim 7

Method claim 7 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it recites the efficacy of the nanoemulsion vaccine, which permits a subject exposed to *B. anthracis* to remain asymptomatic.

H. Dependent Claim 8

Method claim 8 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it recites the efficacy of the nanoemulsion vaccine, where the *B. anthracis* immune response has an rPA specific Th1 type cell mediated immune response, said response exhibiting at least a 3 fold increased expression of IFN-γ in the subject administered the vaccine compared to a control subject.

"Interferon gamma (IFN-γ) is a cytokine critical to both innate and adaptive immunity, and functions as the primary activator of macrophages, in addition to stimulating natural killer cells and neutrophils."[2] " IFN-γ, a cytokine strongly associated with a Th1 response, is an important regulator of the production of IgG2a antibody, a subclass frequently associated with a pathogenic autoantibody response, while IgG1 production (promoted by IL-4) predominates in a Th2 response."[3]

I. Dependent Claim 9

Method claim 9 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it recites the efficacy of the nanoemulsion vaccine, where instead of the LeTx specific neutralizing antibody titer being at least a 100 fold greater in a vaccinated subject than that generated in a control subject contrasted with the 10 fold increase of claim 1. As will be argued *infra*, this is a vague limitation.

[2] *www.sciencedirect.com*
[3] "Paradoxical Roles of INF-ɣ in Models of Th1 mediated," *http://arthritis-research/biomedcentral.com*

J. Dependent Claim 10

Method claim 11 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it recites the efficacy of the nanoemulsion vaccine, where instead of the LeTx specific neutralizing antibody titer being at least a 500 fold greater in a vaccinated subject than that generated in a control subject contrasted with the 10 fold increase of claim 1 and a 100 fold increase of claim 9. As will be argued *infra*, this is a vague limitation.

K. Dependent Claim 11

Method claim 11 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it recites the efficacy of the nanoemulsion vaccine, where instead of the LeTx specific neutralizing antibody titer being at least a 1,000 fold greater in a vaccinated subject than that generated in a control subject contrasted with the 10 fold increase of claim 1, a 100 fold increase of claim 9, and a 500 fold increase of claim 10. As will be argued *infra*, this is a vague limitation.

L. Dependent Claim 12

Method claim 12 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it imposes a limitation on the ingredients of the vaccine component of the composition. It

specifies that the amount of rPA is between 20-100 μg of rPA. Contrast this with claim 4 where the amount of rPA is between 1 and 500 μg of rPA.

M. Dependent Claim 13

Method claim 5 depends from claim 1, and it incorporates all of the limitations of claim 1 therein. Although ostensibly a method claim, it imposes a limitation on the composition of the nanoemulsion vaccine such that the vaccine component is 10% of the nanoemulsion solution. Contrast claim 13 with claim 5, where the vaccine component is within the range of 5% to 20% of the nanoemulsion solution.

N. Independent Claim 14

This is a method claim directed to inducing an immune response to *Bacillus anthracis* (*B. anthracis*), a source of infection commonly known as anthrax. The preamble is limiting because it is specific to producing the immune response to the particular antigen. There are a number of limitations contained in claim 14.

1. Administration

The vaccine must be administered intranasally.

2. Composition of the Vaccine

a. Nanoemulsion Adjuvant

The nanoemulsion adjuvant of claim 14 comprises (1) oil; (2) water; (3) ethanol; (4) a polysorbate surfactant; and (cetylpyridinium chloride (CPC). The

polysorbate surfactant is selected from a Markush group consisting of "polyoxyethylene sorbitan monooleate and polyoxyethylene monolaurate. CPC is a cationic surfactant. This is the same nanoemulsion composition recited in claim 1.

b. The Vaccine Component

The vaccine component is specified as the recombinant protective antigen (rPA) of *B. anthracis*. This is the same vaccine component recited in claim 1.

3. Efficacy

Subjects vaccinated with the *B. anthracis* vaccine allows subjects to survive when challenged with a lethal dose of *B. anthracis*. Note that claim 14 does not include comparison with a control subject as in claim 1.

VIII. THE CHALLENGED CLAIMS ARE NOT ENTITLED TO A PRIORITY DATE EARLIER THAN APRIL 13, 2006.

The '279 Patent results from allowance of U.S. Patent Application No. 11/786,861 (filed on April 13, 2007), which is the nonprovisional counterpart of U.S. Provisional Application No. 60/791,759 (filed on April 13, 2006). The '279 Patent claims priority to the filing date of said provisional application. The closest relevant prior publications by the inventors of the '279 Patent were published earlier than one-year prior to filing said provisional application. Thus, even though the '861 Application was filed pre-AIA, those prior publications of the inventors must be considered prior art citable against the '279 Patent. Therefore, the earliest priority date available to the '279 Patent is April 13, 2006.

IX. OVERVIEW OF THE PRIOR ART

A. **Lowell** (Exhibit 1004)

U.S. Patent 5,961,970 discloses the use of submicron emulsions as vaccine adjuvants. As discussed *supra*, the terms "submicron emulsion" and "nanoemulsion" are equivalent in meaning. Lowell's adjuvant is an oil-in-water nanoemulsion that also comprises an emulsifier, a polysorbate surfactant (*e.g.,* TWEEN) and a C3-C6 alcohol. Lowell's vaccine may be administered topically, and in the eye, the nose, the mouth, and other mucosal surfaces. The droplet size is between 0.03-0.5 μm. Lowell discloses that his vaccine is useful *inter alia* for HIV, Staphylococcal Enterotoxin B (SEB), Leishmania Parasite, and *Shigella flexneri*.

B. **Yaghmur** (Exhibit 1005)

Yaghmur discloses the inclusion of short chain alcohols (*e.g.*, ethanol) and glycerol in microemulsions. As discussed *supra*, the terms "microemulsion" and "nanoemulsion" are equivalent in meaning.

C. **Wright** (Exhibit 1006)

U.S. Patent 5,618,840 discloses antibacterial oil-in-water emulsions contained in droplets that are approximately one micron in diameter. Wright's emulsion was used to inhibit the growth of *Helicobacter Pylori*. Among the ingredients in Wrights emulsion is cetylpyridinium chloride (CPC).

D. **Williamson** (Exhibit 1007)

Williamson discloses immunization with a vaccine containing the recombinant protective antigen (rPA) from *B. anthracis*. The article discloses that

the vaccine rPA component produces a systemic IgG response, and that it creates an immune response that permits a subject to survive a lethal *B. anthracis* challenge and that prevents a subject from displaying signs or symptoms of *B. anthracis* infection upon subsequent exposure to live *B. anthracis*.

E. Baker S292 JACI (Exhibit 1008)

This reference by Baker, *et.al.* was published in 2004 by the inventors of the '279 Patent, and it advocates the use of a nanoemulsion vaccine comprising recombinant *B. anthracis* rPA. It discloses that intranasal administration of the vaccine produces a mucosal IgA response to the rPA of *B. anthracis*. It states, "rPA specific splenocyte activation was demonstrated by proliferative responses in vitro, and was accomplished by markedly increased production of INF-ɣ and TNFσ **...**"

F. Baker '412 (Exhibit 1009)

U.S. Patent Application Publication No. 2003/0194412 A1, published by the USPTO on October 16, 2003, publishes the application 10/162,970 that matured into U.S. Patent 7,314,624. Baker '412 discloses an immunogen combined with a nanoemulsion adjuvant comprising oil, water, ethanol, a polysorbate surfactant (TWEEN-20), and CPC. It teaches the use of nanoemulsion adjuvants as delivery systems for a wide variety of vaccines.

X. GROUNDS FOR PETITION

A. Ground 1: Claim 1 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell (Exhibit 1004) in view of Yaghmur (Exhibit 1005), Wright (Exhibit 1006), and Williamson (Exhibit 1007), and further in view of Baker S292 JACI (Exhibit 1008).

Independent claim 1 is a method claim that recites induction of an immune response to *Bacillus anthracis* (*B. anthracis*) *via* nasal administration of an immunogenic composition to a subject, said composition comprising:

A) a nanoemulsion adjuvant, and

B) a recombinant protective antigen (rPA) of *B. anthracis*.

Lowell teaches the use of submicron emulsions as vaccine adjuvants. As discussed *supra*, the terms, "submicron emulsion" and "nanoemulsion" are equivalent in meaning. Lowell teaches that vaccines contained within nanoemulsions may be administered intranasally (*See* claim 25).

However, the nanoemulsion of claim 1 of the subject '279 Patent comprises:

1. oil;
2. water;
3. ethanol;
4. a polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
5. cetylpyridinium chloride (CPC).

1. <u>The nanoemulsion adjuvant component</u>:

Lowell's adjuvant is a nanoemulsion comprising oil and water (at 2:38), a polysorbate surfactant (at 4:41 — TWEEN-80, *i.e.*, polyoxyethylene (20) sorbitan monooleate). Lowell teaches the use of a nanoemulsion comprising a C3-C6 alcohol. However, ethanol is a C2 alcohol. Yet, Yaghmur teaches a nanoemulsion that comprises ethanol. (*See* Abstract.) Yaghmur's nanoemulsion is suitable as a less toxic adjuvant ("delivery system" at pg 72).

But, Lowell is silent regarding inclusion of CPC. However, Wright teaches an anti-microbial nanoemulsion adjuvant (at 4:23) comprising CPC (at 2:50).

2. <u>The vaccine component</u>:

The vaccine component of claim 1 comprises a recombinant protective antigen (rPA) of *B. anthracis*. However, Williamson teaches the use of a recombinant protective antigen (rPA) of *B. anthracis* as a vaccine. Lowell teaches the use of nanoemulsion adjuvants as delivery systems for a wide variety of vaccines. But, Lowell is silent regarding using nanoemulsions for delivery of anthrax vaccines. Nevertheless, it would have been obvious to a person of ordinary skill in the art at the time of invention to combine the teachings of Lowell, Yaghmur, and Wright with those of Williamson to produce the anthrax vaccine of the '279 Patent, because it would be expected that a mere substitution of one known vaccine component for another should produce predictable results.

In addition, Baker S292 JACI is prior art published in 2004 by the inventors of the subject '279 Patent , and it advocates the use of a nanoemulsion vaccine comprising recombinant *B. anthracis* Protective Antigen (rPA).

However, claim 1 imposes an additional condition "wherein the administering generates a *B. anthracis-specific* immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that is at least 10 fold greater than the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline."

Experimentation discussed in the specification of the '279 Patent revealed that, "no seropositive mice were found in animals intranasally immunized with rPA in saline (See FIG. 3A)." (At 55:6).

To speak of an antibody titer of a Sample A being 10 fold greater than that of a Sample B, one would use the ration formula:

$$\frac{\text{Titer}_A}{\text{Titer}_B}$$

and that ratio would equal 10. No other computation would make sense.

- Titer_A represents the (LeTx)-specific neutralizing antibody titer, and
- Titer_B represents the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline.

If there was no seropositive response in animals immunized with rPA in saline, then $\text{Titer}_B = 0$. Division by zero is a prohibited operation. Thus, the above ratio is meaningless.

Even if the ratio formula were to be:

$$\frac{\log \text{Titer}_A}{\log \text{Titer}_B},$$

it should be noted that the logarithm of zero in the denominator is undefined.

Thus, the condition in claim 1 following the word, "wherein," is meaningless, and it should be ignored.

Therefore, it would have been obvious to a person having ordinary skill in the art to combine the teachings of Lowell, Yaghmur, and Wright with those of Williamson and Baker S292 JACI to produce the anthrax vaccine of claim 1, thus making claim 1 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

B. Ground 2: Alternatively, claim 1 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 (Exhibit 1009) in view of Williamson, and further in view of Baker S292 JACI.

As discussed *supra*, independent claim 1 is a method claim reciting induction of an immune response to *Bacillus anthracis* (*B. anthracis*) *via* nasal administration of an immunogenic composition to a subject, said composition comprising:

A) a nanoemulsion adjuvant, and

B) a recombinant protective antigen (rPA) of *B. anthracis*.

However, the nanoemulsion of claim 1 of the subject '279 Patent comprises:

1. oil;
2. water;
3. ethanol;

4. a polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
5. cetylpyridinium chloride (CPC).

Baker '412 teaches an immunogen combined with a nanoemulsion adjuvant comprising oil [at 0012], water [at 0013], ethanol [at 0140], TWEEN 20, a polysorbate surfactant that is polyoxyethylene (20) sorbitan monolaurate [*see* Figure 4], and cetylpyridinium chloride (CPC) [at 0140].

As in Lowell, Baker '412 teaches a nanoemulsion vaccine comprising a generalized immunogen. However, Williamson teaches the use of a recombinant protective antigen (rPA) of *B. anthracis* as a vaccine. Baker '412 teaches the use of nanoemulsion adjuvants as a delivery system for a wide variety of vaccines.

Yet, Baker '412 is silent regarding using nanoemulsions for delivery of anthrax vaccines. It would have been obvious to a person of ordinary skill in the art at the time of filing the priority application resulting in the subject '279 Patent to combine the teachings of Baker '412 with those of Williamson to produce the anthrax vaccine of the '279 Patent, because it would be expected that a substitution of one known vaccine component for another should produce predictable results.

In addition, as argued *supra*, Baker S292 JACI is prior art published by the inventors of the subject '279 Patent in 2004, and it advocates the use of a nanoemulsion vaccine comprising recombinant *B. anthracis* Protective Antigen (rPA).

Both the Baker '412 and Baker S292 JACI references were available to the Examiner of the application of the subject '279 Patent, and they were considered by him. Williamson was not disclosed to the Examiner, nor does it appear that this reference was considered by the Examiner. In the prosecution history of the subject '279 Patent, the Examiner issued a rejection of claim 1 under 35 U.S.C. 103 as being obvious and unpatentable over Baker '412 in view of Baker S292 JACI. To overcome that rejection, claim 1 was amended to include the condition:

> *wherein the administering generates a B. anthracis-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that is at least 10 fold greater than the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline.*

Unfortunately, the Examiner did not probe further into the implications of this condition, and claim 1 was allowed.

Regarding the condition following the term, "wherein," as argued *supra*, because the inventors found that, "no seropositive mice were found in animals intranasally immunized with rPA in saline," the computed antibody titer of the rPA suspended in saline would be zero.

As argued *supra*, considering that computation of a 10 fold greater quantity is necessarily a ratio, and that the denominator of that ratio is necessarily zero, the computed ratio is meaningless because division by zero is prohibited. Further, even if the computed ratio were to be logarithmic, the logarithm of zero is undefined, thus also making the ratio meaningless. Therefore, the condition following the term, "wherein," is itself meaningless and

should be ignored. Respectfully, reason dictates that the Examiner should not have allowed claim 1, and its obviousness rejection should have been retained.

Therefore, it would have been obvious to a person having ordinary skill in the art to combine the teachings of Baker '412 in view of Williamson, and further in view of Baker S292 JACI, to produce the anthrax vaccine of claim 1 of the '279 Patent, thus making claim 1 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

C. Ground 3: Claim 2 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur (Exhibit 1005), Wright, and Williamson, and further in view of Baker S292 JACI.

Claim 2 depends from claim 1. Thus, according to 35 U.S.C. § 112(d), claim 2 incorporates by reference all of the limitations of claim 1. The vaccines of claims 1 and 2 are administered nasally. As argued *supra*, claim 1 is obvious and unpatentable under 35 U.S.C. § 103. Claim 2 adds the condition, "contacting the nasal mucosal surface of said subject with said composition. However, Lowell's vaccine (which may be administered nasally) recites this condition at 3:23 - 3:33.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time of filing the priority application resulting in the subject '279 Patent to combine the teachings of Lowell, Yaghmur, and Wright with those of Williamson and Baker S292 JACI to produce the anthrax vaccine of claim 1 of

the '279 Patent, thus making claim 1 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

D. Ground 4: Claim 3 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 in view of Williamson, and further in view of Baker S292 JACI.

Claim 3 depends from claim 1. Thus, according to 35 U.S.C. § 112(d), claim 3 incorporates by reference all of the limitations of claim 1. In the Notice of Allowability of September 21, 2018, the Examiner stated, "[t]he allowed claim(s) is/are: 1-2, 10-11, 13, 17, 33, 37-39 and 41-43 renumbered 1-14 respectively." However, the number of allowed claims total 13, not 14. Claim 3 was renumbered from original claim 8, the rejection for which was still maintained. Thus, current claim 3 was not an allowed claim. However, it somehow made its way into the subject '279 Patent. This claim was rejected as late as January 16, 2018 (*i.e.,* the office action just prior to the Notice of Allowance).[4] The '279 Patent included the rejected claim 8, which was renumbered to claim 3. The Notice of Allowability presented no rationale for allowance of this claim.

Claim 3 limits claim 1 "wherein the *B. anthracis* specific immune response comprises a systemic IgG response to said rPA of *B. anthracis* and a mucosal IgA response to said rPA of *B. anthracis.*"

Williamson teaches that the vaccine rPA component of *B. anthracis* produces a systemic IgG response (*see* Abstract). It would have been obvious to

[4] NOTE that the rejection of Jan. 16, 2018 included claim 8. However, in the Notice of Allowability of September 21, 2018, claim 8 was not one of the allowed claims.

a person of ordinary skill that mere combination of the vaccine component of Williamson with the nanoemulsion component of claim 1 would also induce a systemic IgG response.

Further, Baker S292 JACI indicates that intranasal administration of the composition of claim 1 produces a mucosal IgA response to said rPA of *B. anthracis.* Thus, both the systemic IgG and mucosal IgA responses were anticipated by the prior art references.

The Examiner was aware of the Baker '412 and Baker S292 JACI references, but was not made aware of Williamson. Given the explicit statements in these references along with the arguments that claim 1 is obvious over the Baker references, it would not have been reasonable to allow claim 3 to be included in the '279 Patent. And in fact, claim 3 (renumbered from original claim 8) was not one of the allowed claims.

Thus, as in claim 1, claim 3 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 in view of Williamson, and further in view of Baker S292 JACI.

E. Ground 5: Claims 4, 5, 12, and 13 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur, Wright, and Williamson, and further in view of Baker S292 JACI.

Claims 4, 5, 12, and 13 depend from claim 1. Thus, according to 35 U.S.C. § 112(d), claims 4, 5, 12, and 13 incorporate by reference all of the

limitations of claim 1. As argued *supra*, claim 1 is obvious and unpatentable under 35 U.S.C. § 103(a).

Claim 4 adds the limitation, that the "immunogenic composition comprises between 1 and 500 µg of said rPA."

Claim 5 adds the limitation that the "immunogenic composition comprises 5%-20% nanoemulsion solution."

Claim 12 adds the limitation that the "immunogenic composition comprises "20-100 µg of said rPA."

Claim 13 adds the limitation that the "immunogenic composition comprises "a 10% nanoemulsion solution."

The additional limitations to those of claim 1 contained in claims 4, 5, 12, and 13 represent mere variation of the different parameters of the process that produced the immunogenic composition. This variation was within the scope of what a person having ordinary skill in the art would perform during routine experimentation. There is no disclosed indication that the specific range limitations of these claims resulted in unexpected results, nor that selection of said limitations was anything out of the ordinary. "More particularly, where the general conditions of a claim is disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *Application of Aller*, 220 F.2d 233, 235 (C.C.P.A. 1955).

Further, in *KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 401 (2007), regarding patent claims "based on the combination of elements found in the prior art," the Supreme Court held that,"[s]uch a combination of familiar elements

according to known methods is likely to be obvious when it does no more than yield predictable results." Here, the inventors combined the ingredients of claim 1 using known experimental methods to produce optimum results that were predictable. The limitations of claims 4, 5, 12, and 13 add little to those of claim 1 that a person of ordinary skill would not have discovered by routine experimentation.

Thus, because the limitations of claims 4, 5, 12, and 13 do not represent inventive activities beyond what a person having ordinary skill in the art would perform by routine experimentation, and because these claims incorporate the limitations of claim 1 therein, based on the same arguments for obviousness and unpatentability of claim 1, claims 4, 5, 12, and 13 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur, Wright, and Williamson, and further in view of Baker S292 JACI.

F. Ground 6: Claims 6 and 7 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur, Wright, and Williamson, and further in view of Baker S292 JACI.

Claim 6 depends from claim 1. Thus, according to 35 U.S.C. § 112(d), claim 6 incorporates by reference all of the limitations of claim 1. In addition to the limitations of claim 1, claim 6 adds the limitation, "wherein said *B. anthracis* specific immune response permits said subject to survive a lethal *B. anthracis* challenge."

Claim 7 depends from claim 1. Thus, according to 35 U.S.C. § 112(d), claim 7 incorporates by reference all of the limitations of claim 1. In addition to the limitations of claim 1, claim 7 adds the limitation, "wherein said *B. anthracis* specific immune response prevents said subject from displaying signs or symptoms of *B. anthracis* infection upon subsequent exposure of said subject to live *B. anthracis.*"

However, Williamson teaches that his *B. anthracis* vaccine creates an immune response that permits said subject to survive a lethal *B. anthracis* challenge (as in claim 6 of the '279 Patent) and that prevents said subject from displaying signs or symptoms of *B. anthracis* infection upon subsequent exposure of said subject to live *B. anthracis* (as in claim 7 of the '279 Patent). He states:

> *All the immunized animals survived challenge without any symptoms of infection. A single control animal which had been treated with alhydrogel in saline died. Postchallenge, the immunized macaques were monitored for bacteremia and expected clinical signs for 1 month postchallenge, none of which were observed.*
> (*see* Pg. 14, "(b) Protection against challenge.")

The only animal that died or displayed symptoms when challenged with *B. anthracis* is the one control subject not treated with Williamson's vaccine. It would have been obvious to a person having ordinary skill in the art that mere combination of the vaccine component of Williamson with the nanoemulsion adjuvant of claim 1 should have similar results.

Therefore, it would have been obvious to a person having ordinary skill in the art to combine the teachings of Lowell, Yaghmur, and Wright with those of

Williamson and Baker S292 JACI to produce the anthrax vaccine having the limitations of claims 6 and 7 over claim 1, thus making claims 6 and 7 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

G. Ground 7: Claim 8 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 in view of Williamson, and further in view of Baker S292 JACI.

Claim 8 depends from claim 1. Thus, according to 35 U.S.C. § 112(d), claim 6 incorporates by reference all of the limitations of claim 1. In addition to the limitations of claim 1, claim 8 adds the following limitation:

> wherein said *B. anthracis* specific immune response comprises a rPA-specific Th1 type cell mediated immune response comprising at least a 3 fold increased expression of IFN-ϒ in said subject compared to a control subject not administered said immunogenic composition.

Figure 15 of Baker '412 shows early cytokine responses in splenocytes and serum of mice 82 hours after treatment with influenza A-100 pfu/mouse, formalin-killed virus 5xl0^5 pfu, virus (5x10^5 pfu)/2% nanoemulsion mixture, nanoemulsion alone. Figure 15A of Baker '412 shows a dramatically greater than 3 fold increased expression of IFN-γ (type II interferon) in a subject to which the nanoemulsion vaccine was administered nasally compared to a subject not administered an immunogenic composition. The nanoemulsion adjuvant of Baker '412 is identical to that of claim 1 of the '279 Patent. However, Baker '412 is silent regarding administration of the *B. anthracis* nanoemulsion vaccine component of claim 1.

Nevertheless, Baker S292 JACI states, "rPA specific splenocyte activation was demonstrated by proliferative responses in vitro and was accompanied by markedly increased production of INF-γ and TNFσ, **... ".** It would have been obvious to a person having ordinary skill in the art that mere substitution of the vaccine component of Baker S292 JACI with the nanoemulsion adjuvant of claim 1 would have similar results.

As mentioned *supra*, the Examiner was aware of the Baker '412 and Baker S292 JACI references. Respectfully, claim 8 should not have been allowed in light of the above arguments.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time of filing to combine the teachings of Baker '412 in view of Williamson, and further in view of Baker S292 JACI, as in claim 1, to produce the anthrax vaccine having the limitation of claim 8 over claim 1, thus making claim 8 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

H. Ground 8: Claims 9, 10, and 11 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur, Wright, and Williamson, and further in view of Baker S292 JACI.

Claims 9, 10, and 11 depend from claim 1. Thus, according to 35 U.S.C. § 112(d), claims 9, 10, and 11 incorporate by reference all of the limitations of claim 1. Claim 9 recites:

> *The method of claim **1,** wherein said LeTx-specific neutralizing antibody is at least 100 fold greater than the LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline.*

This recitation in claim 9 is identical to the "wherein" clause of claim 1, except that the words, "10 fold greater," have been replaced by the words, "100 fold greater." The recitation in claim 10 replaces those words with "500 fold greater," and the recitation in claim 11 replaces those words with "1000 fold greater." Otherwise, the claims are identical.

As discussed supra, experimentation discussed in the specification of the '279 Patent revealed that, "no seropositive mice were found in animals intranasally immunized with rPA in saline (See FIG. 3A)." (At 55:6). As put forth in the arguments regarding claim 1, *supra*, the specific limitations in claims 9, 10, and 11 are meaningless as in claim 1, because they either employ prohibited divisions by zero or utilize an undefined logarithm of zero in the denominator of a ratio. There is nothing to measure the increased antibody titer against.

Thus, claims 9, 10, and 11 are obvious to a person having ordinary skill in the art because those claims incorporate all of the limitations of claim 1 therein, and the conditions for obviousness are not altered by the meaningless conditions of these dependent claims. Therefore, claims 9, 10, and 11 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur, Wright, and Williamson, and further in view of Baker S292 JACI.

I. Ground 9: Alternatively, claims 9, 10, and 11 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 in view of Williamson, and further in view of Baker S292 JACI.

Claims 9, 10, and 11 depend from claim 1. Thus, according to 35 U.S.C. § 112(d), claims 9, 10, and 11 incorporate by reference all of the limitations of claim 1.

While claim 1 recites an "LeTx-specific neutralizing antibody is at least 10 fold greater than the LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline," claim 9 recites a 100 fold increase, claim 10 recites a 500 fold increase, and claim 11 recites a 1000 fold increase.

As argued in claim 1, *supra*, because "no seropositive mice were found in animals intranasally immunized with rPA in saline," the specific limitations in claims 9, 10, and 11 are meaningless as in claim 1. They either employ prohibited divisions by zero or utilize an undefined logarithm of zero in the denominator of a ratio. There is nothing to measure the increased antibody titer against.

Respectfully, although the Examiner was aware of Baker '412 and Baker S292 JACI, reason dictates that claims 9, 10, and 11 should not have been allowed.

Thus, claims 9, 10, and 11 are obvious to a person having ordinary skill in the art because those claims incorporate all of the limitations of claim 1 therein, and the conditions for obviousness are not altered by the meaningless conditions of these dependent claims. Therefore, claims 9, 10, and 11 are obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 in view of Williamson, and further in view of Baker S292 JACI.

J. Ground 10: Claim 14 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Lowell in view of Yaghmur, Wright, and Williamson, and further in view of Baker S292 JACI.

Independent claim 14 is a method claim reciting induction of an immune response to *Bacillus anthracis* (*B. anthracis*) *via* nasal administration of an immunogenic composition to a subject, said composition comprising:

A) a nanoemulsion adjuvant, and

B) a recombinant protective antigen (rPA) of *B. anthracis*.

As argued with regard to claim 1, Lowell teaches the use of submicron emulsions as vaccine adjuvants. Lowell teaches that vaccines contained within nanoemulsions may be administered intranasally.

However, as in claim 1, the nanoemulsion in claim 14 of the '279 Patent comprises:

1. oil;
2. water;
3. ethanol;
4. a polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
5. cetylpyridinium chloride (CPC).

1. <u>The nanoemulsion adjuvant component</u>:

Lowell's adjuvant is a nanoemulsion comprising oil and water (at 2:38), a polysorbate surfactant (at 4:41 — TWEEN-80, *i.e.*, polyoxyethylene (20) sorbitan

monooleate). However, Lowell teaches the use of a nanoemulsion comprising a C3-C6 alcohol. Ethanol is a C2 alcohol. Yet, as argued regarding claim 1, *supra*, Yaghmur teaches a nanoemulsion that comprises ethanol. Yaghmur's nanoemulsion is suitable as a less toxic adjuvant ("delivery system").

Lowell is silent regarding inclusion of CPC. However, Wright teaches an anti-microbial nanoemulsion adjuvant (at 4:23) comprising CPC (at 2:50).

2. <u>The vaccine component</u>:

As in claim 1, the vaccine component of claim 14 comprises a recombinant protective antigen (rPA) of *B. anthracis*. But, Williamson teaches the use of a recombinant protective antigen (rPA) of *B. anthracis* as a vaccine. Lowell taught the use of nanoemulsion adjuvants as a delivery system for a wide variety of vaccines. However, Lowell is silent regarding using nanoemulsions for delivery of anthrax vaccines. It would have been obvious to a person of ordinary skill in the art to combine the teachings of Lowell, Yaghmur, and Wright with those of Williamson to produce the anthrax vaccine of claim 14, because it would be expected that a mere substitution of one known vaccine component for another should produce predictable results.

In addition, Baker S292 JACI advocates the use of a nanoemulsion vaccine comprising recombinant *B. anthracis* Protective Antigen (rPA).

However, claim 14 imposes an additional condition:

> *wherein the administering generates a B. anthracis-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that permits said subject to survive a lethal B. anthracis challenge.*

But, Williamson recites a vaccine component that permits a subject to survive a lethal *B. anthracis* challenge. It would have been obvious to a person having ordinary skill in the art at the time of invention of the '279 Patent that the mere addition of the nanoemulsion adjuvant of claim 1 would probably not diminish the survivability. In fact, the utility of the Present Invention would rely on enhancement of the ability of the subject to survive a lethal *B. anthracis* challenge.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time of filing the priority application resulting in the subject '279 Patent to combine the teachings of Lowell, Yaghmur, and Wright with those of Williamson and Baker S292 JACI to produce the anthrax vaccine of claim 14 of the '279 Patent, thus making claim 1 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

K. Ground 11: Alternatively, claim 14 is obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over Baker '412 (Exhibit 1009) in view of Williamson, and further in view of Baker S292 JACI.

As discussed *supra*, independent claim 14 is a method claim reciting induction of an immune response to *Bacillus anthracis* (*B. anthracis*) *via* nasal administration of an immunogenic composition to a subject, said composition comprising:

A) a nanoemulsion adjuvant, and

B) a recombinant protective antigen (rPA) of *B. anthracis*.

Baker '412 teaches an immunogen combined with a nanoemulsion adjuvant comprising oil [at 0012], water [at 0013], ethanol [at 0140], TWEEN 20, a polysorbate surfactant that is polyoxyethylene (20) sorbitan monolaurate [*see* Figure 4], and cetylpyridinium chloride (CPC) [at 0140]. Therefore, the nanoemulsion adjuvant of claim 14 of the '279 Patent is taught in Baker '412.

As in Lowell, Baker '412 teaches a nanoemulsion vaccine comprising a generalized immunogen. However, Williamson teaches the use of a recombinant protective antigen (rPA) of *B. anthracis* as a vaccine. Baker '412 teaches the use of nanoemulsion adjuvants as a delivery system for a wide variety of vaccines. But, Baker '412 is silent regarding using nanoemulsions for delivery of anthrax vaccines. It would have been obvious to a person having ordinary skill in the art to combine the teachings of Baker '412 with those of Williamson to produce the anthrax vaccine of claim 14 of the '279 Patent, because it would be expected that a substitution of one known vaccine component for another should produce predictable results.

In addition, as argued *supra*, Baker S292 JACI is prior art published by the inventors of the subject '279 Patent in 2004, and it advocates the use of a nanoemulsion vaccine comprising recombinant *B. anthracis* Protective Antigen (rPA).

Both the Baker '412 and Baker 292 JACI references were available to the Examiner of the application of the subject '279 Patent, and they were considered

by him. In the prosecution history of the subject '279 Patent, the Examiner issued a rejection of claim 1 under 35 U.S.C. 103 as being obvious and unpatentable over Baker '412 in view of Baker 292 JACI. However, independent claim 14 was a new claim added on July 16, 2018 after the final rejection mailed to the Applicants on January 16, 2018. Claim 14 did not contain the 10 fold increase in antibody titer that was recited in claim 1. The USPTO issued no further office actions before the Notice of Allowance mailed on September 21, 2018.

In the Notice of Allowability of September 21, 2018, the Examiner recited the entirety of claim 1[5] in the reasons for allowance, stating:

> *The closest prior art, Baker et al. (Journal of Allergy and Clinical Immunology, vol. 113, no. 2, S292, February 2004)*[6] *and further in view of Baker et al. (U.S. Patent 7314624)*[7] *hereinafter called Baker et al. 2002 and further in view of Hanson et al. Clin Vaccine Immunol. 2006 Feb; 13(2); 208-213 fails to anticipate or make obvious the above claims.*

The Examiner made no mention of independent claim 14 (renumbered from claim 43). No mention was made of the Williamson reference (Exhibit 1007) in the subject '279 Patent, nor is there any indication if the Examiner's awareness of this reference.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time of filing the priority application resulting in the subject '279 Patent to combine the teachings of Baker '412 in view of Williamson, and further in view of Baker S292 JACI, to produce the anthrax vaccine of claim 14 of the '279

[5] inclusive of the *wherein* clause reciting the 10 fold increase in antibody titer
[6] Baker S292 JACI (Exhibit 1008)
[7] Baker '412 (Exhibit 1009) is the application publication of U.S. Patent 7,314,624.

Patent, thus making claim 14 unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a).

XI. THE BOARD SHOULD INSTITUTE AN IPR

No prior IPRs have been filed against the ’279 Patent by Trutek Corp.

The '279 Patent is assigned to the Regents of the University of Michigan. Although the matter pending in the Eastern District of Michigan is unrelated to the '279 Patent, according to information and belief, the inventors listed on the patent are associated with BlueWillow Biologics, Inc., and that business entity is utilizing the technology disclosed and claimed in the '279 Patent.

The earliest priority date for the '279 Patent is April 13, 2006. Although the Examiner cited the U.S. Patent 7,314,624 as prior art in the prosecution history of the '279 Patent, that citation was not prior art, as it was issued on January 1, 2008. Nonetheless, the Examiner was aware of the '412 Application, which published in 2003, because it was listed on the '624 Patent. Further, the Examiner cited Baker S292 JACI as prior art. However, the Examiner was apparently unaware of the Lowell, Wright, Yaghmur, and Williamson prior art references.

Given the commonality and well known use of the active and inactive ingredients of the '279 Patent's claims, the Examiner incorrectly relied on the cited prior art references, and he was unaware of the other non-cited prior art references cited herein. The '279 Patent is not entitled to a priority date earlier than April 13, 2006. Petitioner presented six references that were published prior

to April 13, 2006. Claims 1-14 were shown to be obvious and unpatentable under 35 U.S.C. § 103 or pre-AIA 35 U.S.C. § 103(a) over the cited prior art. Claim 3 was not an allowed claim, but it subsequently appeared in the '279 Patent. Despite this fact, claim 3 would be allowable as a dependent claim if its base claim 1 were also allowable. However, as argued *supra*, claim 1 is obvious and unpatentable. Further, the Examiner provided no rationale for allowance of independent claim 14, which is also obvious and unpatentable.

XII. CONCLUSION

Petitioner requests institution of an IPR and cancellation of the Challenged Claims.

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R. §42.24, totaling 9,867 words. Counsel has relied upon the word count feature provided by Microsoft Word.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,138,279 (and accompanying Exhibits) by first class mail on the Patent Owner at the correspondence address of the Patent Owner as follows:

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