UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner
v.
GLAXOSMITHKLINE BIOLOGICALS S.A.,
Patent Owner

CASE IPR: Unassigned

PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 9,422,345

Claims 1-2, 4-14, and 16-21

UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

(Retallack *et al.*)

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TABLE OF ABBREVIATIONS

BLAST	Basic Local Alignment Search Tool
BRC	broadest reasonable construction
CRM	cross-reacting material
CSP	consensus signal peptide
DTx	diphtheria toxin
IPR	*Inter partes* review
MCS	multiple cloning site
mRNA	messenger RNA
ORF	open reading frame
POSA	person of ordinary skill in the art
Sec	Secretory
SRP	signal recognition particle

EXHIBIT LIST

Exhibit No.	Description
1001	United States Patent No. 9,422,345 (Blais et al.) ("the '345 patent")
1002	Prosecution History of United States Patent No. 9,422,345 (USSN 13/500,244)
1003	International Publication No. WO 2011/042516A2 published on April 14, 2011 (Blais, et al.) ("PCT-047")
1004	Great Britain Patent Application No. 0917647.0 (GlaxoSmithKline Biologicals S.A.) ("GB-647")
1005	United States Patent No. 6,455,673 (Collier) ("Collier-1")
1006	Declaration of Matthew P. DeLisa, Ph.D. dated November 2, 2018
1007	United States Patent Application Publication No. US2003/0157093A1 (Neville, Jr., et al) ("Neville")
1008	Huber, et al., "Use of Thioredoxin as a Reporter to Identify a Subset of *Escherichia coli* Signal Sequences That Promote Signal Recognition Particle-Dependent Translocation," *J. Bacteriol. 187*(9), 2983-91 (May 2005) ("Huber")
1009	International Publication No. WO 2011/123139A1 (Retallack, et al.) ("Retallack")
1010	United States Patent No. 9,580,719 (Retallack, et al.) ("Retallack-719")
1011	Giannini, et al., "The Amino-Acid Sequence of Two Non-Toxic Mutants of Diphtheria Toxin: CRM45 and CRM197," *Nucleic Acids Research 12*(10), 4063-69 (1984) ("Giannini-1")
1012	pET-22B(+) Vector Map (https://web.archive.org/web/20030819085202/http://www.novagen.com:80/docs/NDIS/69744-000.pdf)
1013	Oh, et al., "Translocation of the Catalytic Domain of Diphtheria Toxin Across Planar Phospholipid Bilayers by Its Own T Domain," *Proc. Natl. Acad. Sci. USA 96*, 8467-70 (July 1999)
1014	Uchida, et al., "Diphtheria Toxin and Related Proteins," *J. Biological Chem. 248*(11), 3838-44 (June 10, 1973)
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1017	HibTITER®, *2007 Physicians' Desk Reference*, 61st ed., 3426-29 (Thomson PDR, Montvale, N.J., 2007)
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1019	Tweten, et al., "Molecular Cloning and Expression of Gene Fragments from Corynebacteriophage β Encoding Enzymatically Active Peptides of Diphtheria Toxin," *J. Bacteriology 156*(2), 680-85 (Nov. 1983)
1020	Terpe, "Overview of Bacterial Expression Systems for Heterologous Protein Production: From Molecular and Biochemical Fundamentals to Commercial Systems," *Appl. Microbiol. Biotechnol. 72*, 211-22 (2006)
1021	Novagen, pET System Manual, 11th ed. (2006)
1022	Lee, et al, "Protein Secretion and the Pathogenesis of Bacterial Infections," *Genes & Development 15*, 1725-52 (Cold Spring Harbor Lab. Press, 2001)
1023	Leong, et al., "Cloned Diphtheria Toxin Fragment A Is Expressed from the *tox* Promoter and Exported to the Periplasm by the SecA Apparatus of *Escherichia coli* K12," *J. Biological Chem. 258*(24), 15016-20 (Dec. 25, 1983)
1024	Lei, et al., "Characterization of the *Erwinia carotovora pelB* Gene and Its Product Pectate Lyase," *J. Bacteriol. 169*(9), 4379-83 (Sept. 1987)
1025	Sletta, et al., "The Presence of N-Terminal Secretion Signal Sequences Leads to Strong Stimulation of the Total Expression Levels of Three Tested Medically Important Proteins During High-Cell-Density Cultivations of *Escherichia coli*," *Applied & Environmental Microbiology 73*(3), 906-12 (Feb. 2007)
1026	Papini, et al., "Diphtheria Toxin and Its Mutant *crm* 197 Differ in Their Interaction with Lipids," *FEBS Letters 215*(1), 73-78 (May 1987)
1027	Ikemura, et al., "Requirement of Pro-Sequence for the Production of Active Subtilisin E in *Escherichia coli*," *J. Biological Chem. 262*(16), 7859-64 (June 5, 1987) ("Ikemura")

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1029	Sambrook, et al., *Molecular Cloning, A Laboratory Manual*, 2nd ed. (Cold Spring Harbor Laboratory Press, U.S.A., 1989)
1030	United States Patent No. 5,917,017 (Collier, et al.) ("Collier-2")
1031	Cohen, et al., "Construction of Biologically Functional Bacterial Plasmids *In Vitro*," *Proc. Nat. Acad. Sci. USA 70*(11), 3240-44 (Nov. 1973)
1032	Kaczorek, et al., "Nucleotide Sequence and Expression of the Diphtheria *tox*228 Gene in *Escherichia coli*," *Science 221*, 855-58 (Aug. 26, 1983)
1033	Lees, et al., "Conjugation Chemistry," *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*, Chap. 11, 163-74 (ASM Press, Washington, D.C., 2008)
1034	United States Patent Application Publication No. US2012/0289688A1 (Blais et al.)
1035	*Merriam-Webster's Collegiate Dictionary*, 10th ed., 168 ("capable") (Merriam-Webster, Incorporated, Springfield, Mass., 1997)
1036	Zhou, et al., "Secretory Expression of Recombinant Diphtheria Toxin Mutants in *B. Subtilis*," *J. Tongji Med. Univ. 19*(4), 253-56 (1999)
1037	Alberts, et al., *Molecular Biology of The Cell*, 5th ed., 128, 130-31, 147, 331-39, 345, 366-69, 532, 540-41, 546-48, 550-51, 617-18 (Garland Science, Taylor & Francis Group, LLC, New York, NY, 2008)
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1040	Van den Berg, et al., "X-Ray Structure of a Protein-Conducting Channel," *Nature 427*, 36-44 (Jan. 2004)
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1050	Giannini, et al., "The Complete Nucleotide Sequence of the Gene Coding for Diphtheria Toxin in the Corynephage Omega (tox+) Genome," *Nucleic Acids Research 11*(19), 6589-95 (1983) ("Giannini-2")
1051	United States Patent Application Publication No. US2008/0193974A1 (Coleman, et al.)
1052	GenBank, "*Escherichia coli* Str. K-12 Substr. MG1655, Complete Genome, showing region from base 1135497 to 1136594," https://www.ncbi.nlm.nih.gov/nuccore/49175990?sat=4&satkey=22394872 (last visited June 29, 2018)
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1055	Greenfield, et al., "Nucleotide Sequence of the Structural Gene for Diphtheria Toxin Carried by Corynebacteriophage *β*," *Proc. Natl. Acad. Sci. USA 80*, 6853-57 (Nov. 1983)
1056	Madigan, et al., *Brock Biology of Microorganisms*, 9th ed., 108, 154-55 (Prentice Hall, Upper Saddle River, N.J., 2000)

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1058	Paetzel, et al., "The Structure and Mechanism of Bacterial Type I Signal Peptidases, A Novel Antibiotic Target," *Pharmacology & Therapeutics 87*, 27-49 (2000)
1059	Talmadge, et al., "Cellular Location Affects Protein Stability in *Escherichia coli*," *Proc. Natl. Acad. Sci. USA 79*, 1830-33 (Mar. 1982)
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1063	Prosecution History excerpt of European Patent Application No. 16192258.8, August 16, 2018 GlaxoSmithKline Response to April 18, 2018 European Patent Office Communication (https://register.epo.org/application?number=EP16192258&d-16544-o=2&Ing=en&tab=doclist&d-16544-s=1)
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1065	Schäffner, et al., "Cosecretion of Chaperones and Low-Molecular-Size Medium Additives Increases the Yield of Recombinant Disulfide-Bridged Proteins," *Applied & Environmental Microbiology 67*(9), 3994-4000 (Sept. 2001)
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1067	Paoletti, et al., "Preclinical Evaluation of Group B Streptococcal Polysaccharide Conjugate Vaccines Prepared with a Modified

Exhibit No.	Description
	Diphtheria Toxin and a Recombinant Duck Hepatitis B Core Antigen," *Vaccine 20*, 370-76 (2002)
1068	Retallack, et al., "Transport of Heterologous Proteins to the Periplasmic Space of *Pseudomonas fluorescens* Using a Variety of Native Signal Sequences," *Biotechnol. Lett. 29*, 1483-91 (2007) ("Retallack (2007)")
1069	Horton, et al., "Gene Splicing by Overlap Extension," *Methods in Enzymology 217*, 270-79 (1993)
1070	Heckman, et al. "Gene Splicing and Mutagenesis by PCR-Driven Overlap Extension," *Nature Protocols 2*(4), 924-32 (2007)
1071	United States Provisional Patent Application No. 61/319,152 (Retallack, et al.) ("Retallack-Provisional")
1072	United States Patent Application Publication No. US2006/0008877A1 (Retallack, et al.) ("'877 Publication")
1073	Declaration of Catharina J. Chin Eng dated November 5, 2018
1074	Declaration of John T. Haines dated October 25, 2018
1075	Merck Press Release, "Pfenex Grants Exclusive License to Merck & Co., Inc. for the Production of Proteins for Undisclosed Vaccine Program," dated December 14, 2009

37 C.F.R. § 42.8 MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

a. ***Related Matters* (37 C.F.R. § 42.8(b)(2))**. Petitioner is concurrently filing another petition for *Inter Partes* Review against the '345 patent on distinct grounds. Petitioner has also filed two petitions for *Inter Partes* Review of U.S. Patent No. 8,753,645 (IPR Nos. 2018-01229 & -01236) and two petitions for *Inter Partes* Review of U.S. Patent No. 9,265,839 (IPR Nos. 2018-01234 & -01237).

b. ***Real Party-In-Interest* (37 C.F.R. § 42.8(b)(1))**. The real parties-in-interest ("RPI") are Petitioner Merck Sharp & Dohme Corp. and Merck & Co., Inc. Petitioner is not barred by operation of estoppel to submit this petition for *inter partes* review.

Patent Owner alleges in the related proceedings that Pfenex, Inc. ("Pfenex") is a RPI to the above-mentioned related matters merely because Patent Owner believes that Pfenex has some interest in Petitioner bringing its V114 product to market. This argument impermissibly expands the RPI requirement. The two questions lying at "the heart" of the RPI inquiry are whether a petition "has been filed at a nonparty's behest" and whether the non-party "desires review of the patent." *Applications in Internet Time, LLC v. RPX Corp.*, 897 F.3d 1336, 1351 (Fed. Cir. 2018). Here, neither factor weighs in favor of a finding that Pfenex is an RPI.

First, the lack of evidence that this petition was filed at the behest of Pfenex, as well as the "practical situation" here – *i.e.*, the *implausibility of* Merck filing this petition to serve Pfenex — make clear that the "RPI behest-of test" is not satisfied. *See AIT*, 897 F.3d at 1349 n.3, 1351. Merck is one of the largest pharmaceutical companies in the world (with $40 Billion in revenue in 2017), and has plans to seek regulatory approval for the sale of its V114 product. Merck is challenging the validity of the '345 patents in anticipation of a future launch of that product. Merck has not filed these petitions at the behest of Pfenex, a small company (with less than $30 Million in revenue in 2017) that has merely licensed Merck technology.

Second, Pfenex is in the business of <u>licensing</u> its Pfenex Expression Technology™. (Exh. 1075). Pfenex has not been, and will not be, involved in making, using, offering for sale, selling or importing Merck's proposed V114 product or any portion of that product. (Exh. 1074, ¶ 6). Licensing technology to Merck is not making, using, offering for sale, selling or importing that technology, and is not otherwise an act of infringement. *See* 35 U.S.C. § 271(a). Instead, it merely authorizes Merck to use that technology without fear of facing an infringement suit *from Pfenex*. Accordingly, Pfenex has no incentive to attack any claim of the challenged patents based on Merck's making, using, offering for sale, selling or importing Merck's proposed V114 product or any portion of that product.

These facts lay in stark contrast to those of *AIT*. The *AIT* Petitioner, RPX, was in the business of challenging patents for other companies. 897 F.3d at 1351-52. RPX filed its petition on behalf of a company, Salesforce.com, that was statutorily time-barred[1] from filing an IPR in its own name. *Id*. at 1353. This was exactly the type of end-run around the IPR estoppel/time bar provisions that the RPI requirement was designed to prevent.

Accordingly, Pfenex is not an RPI to this petition.

c. *Designation of Lead and Back-Up Counsel and Service Information* (37 C.F.R. § 42.8(b)(3)-(4)). Petitioner identifies the following:

- *Lead counsel*: Anthony M. Insogna (Reg. No. 35,203)
  JONES DAY
  4655 Executive Drive, Suite 1500
  San Diego, CA 92121-3134

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[1] There are no time bar issues associated with Merck's petition. Moreover, "if a petition fails to identify all real parties in interest under § 312(a)(2), the Director can, and does, allow the petitioner to add a real party in interest." *Google LLC v. Seven Networks, LLC*, No. IPR2018-01047, Paper 11 at 4 (P.T.A.B. Sept. 25, 2018). Thus, not naming Pfenex as an RPI does not warrant denying institution even if GSK's RPI arguments are valid, which they are not.

Tel: (858) 314-1200
Fax: (844) 345-3178
Email:MerckGSK-IPRs@jonesday.com

- *Back-up counsel*: Nikolaos C. George (Reg. No. 39,201)
Gasper J. LaRosa (Reg. No. 62,477)
Catharina J. Chin Eng (Reg. No. 42,412)
JONES DAY
250 Vesey Street
New York, NY 10281-1047
Tel: (212) 326-3939
Fax: (212) 755-7306
Email: MerckGSK-IPRs@jonesday.com

Arlene L. Chow (Reg. No. 47,489)
Ernest Yakob (Reg. No. 45,893)
HOGAN LOVELLS US LLP
875 Third Avenue
New York, NY 10022
Tel: (212) 918-3000
Fax: (212) 918-3100
Email: MerckIPRs@hoganlovells.com

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") requests *inter partes* review of independent claims 1 and 6, and dependent claims 2, 4-5, 7-14 and 16-21 of U.S. Patent No. 9,422,345 ("the '345 patent") (Exh. 1001), assigned to GlaxoSmithKline Biologicals S.A. ("Patent Owner" or "GSK"). This petition demonstrates that there is a reasonable likelihood that Petitioner will prevail since the prior art renders all the challenged claims anticipated or obvious, under 35 U.S.C. §§ 102 or 103, by a preponderance of the evidence.

For decades, "carrier" proteins have been coupled to polysaccharides to create vaccines that boost human immune response. CRM197 protein is a diphtheria toxin ("DTx") mutant and one of the most well-known carrier proteins in prior art commercial vaccines. The '345 patent claims are directed to polynucleotides that make CRM197 (and related polypeptides at least 90% identical to CRM197) with well-known techniques of bacterial recombinant expression. There is nothing new or nonobvious about the '345 patent claims.

The '345 patent attempts to distinguish itself from the prior art by directing production of CRM197 (and related) proteins into the bacterial periplasm. But, the inventors of the '345 patent did not invent periplasmic expression of proteins (including DTx proteins). The prior art taught the benefit of directing protein transport to the favorable environment of the bacterial periplasm (*e.g.*, for properly folded proteins). Indeed, the state of the art was so well developed in this area that commercial suppliers marketed their polynucleotides to POSAs based on their ability to direct transport of proteins to the periplasm. These polynucleotides were used for producing DTx proteins.

Claim 1 is directed to a polynucleotide with the following well-known features: (1) a "3' portion" (*i.e.* downstream portion) encoding a polypeptide at least 90% identical to CRM197; and (2) a "5' portion" (*i.e.* upstream portion) encoding a signal sequence that is capable of directing transport to the periplasm and is not derived from *C. diphtheriae*. Claim 1 is anticipated or obvious in view of at least two references: Retallack and Retallack-719.

Retallack (Exh. 1009), a WIPO publication of a PCT application filed April 9, 2010,[2] anticipates claim 1. Retallack discloses CRM197 and its production in bacteria. This reference discloses polynucleotides encoding CRM197 and signal sequences, (*e.g.,* from *P. fluorescens*), which are capable of directing periplasmic transport and not derived from *C. diphtheriae*.

[2] As discussed below in Section VII, the '345 patent is not entitled to its October 8, 2009 foreign filing date in Great Britain. Its next earliest filing date is October 7, 2010 and thus Retallack is prior art.

Retallack-719 (Exh. 1010), a United States Patent issuing from an application filed on October 30, 2009,[3] anticipates or alternatively renders obvious claim 1. Retallack-719 teaches polynucleotides comprising a 5' signal sequence portion that encodes a polypeptide, which is capable of directing periplasmic transport and not derived from *C. diphtheriae*, and a 3' toxin portion. It also teaches that one heterologous protein that can be directed to the periplasm using its disclosed polynucleotides is CRM197.

The other claims of the '345 patent do not add any novel and nonobvious features. Claims 2 and 18, which limit the 3' portion of the polynucleotide to those that encode polypeptides having the amino acid sequence of CRM197, are anticipated by Retallack, and anticipated by or rendered obvious by Retallack-719 since both references disclose polynucleotides encoding CRM197.

Similarly, claims 4-14, 16-17 and 20 specify that the 5' portion encodes particularly recited, known signal sequences. Huber (2005) (Exh. 1008) teaches the same signal sequences recited in these claims and demonstrates they are capable of directing transport of a polypeptide to the periplasm. Consequently, POSAs would have been motivated to combine the teaching of both Retallack and Retallack-719

[3] *See* note 2 above and Section VII.

with Huber to arrive at the polynucleotides of claims 4-14, 16-17 and 20 with a reasonable expectation of success.

In view of the foregoing, Petitioner respectfully submits there is at least a reasonable likelihood that it will prevail in showing at least one of the challenged claims is unpatentable. In support of the proposed grounds for unpatentability, this Petition is accompanied by the declaration of Matthew P. DeLisa, Ph.D. (Exh. 1006), an expert in recombinant polypeptide production.

II. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

A. Grounds For Standing

Petitioner certifies that: (1) the ’345 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting review of any claim on the grounds identified in this Petition. 37 C.F.R. § 42.104(a). The Office is authorized to charge all fees due in connection with this matter to Deposit Account No. 50-3013.

B. Identification Of Challenge

Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1-2, 4-14, and 16-21 of the ’345 patent pursuant to the following statement of precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1-2, 18-19 and 21	Pre-AIA 102(e)	• Retallack
II	4-14, 16-17 and 20	Pre-AIA 103	• Retallack • Huber
III	1-2, 18-19 and 21	Pre-AIA 102(e)	• Retallack-719
IV	1-2, 18-19 and 21	Pre-AIA 103	• Retallack-719
V	4-14, 16-17 and 20	Pre-AIA 103	• Retallack-719 • Huber

III. PERSON OF ORDINARY SKILL IN THE ART ("POSA")

The field of the invention is directed to polypeptide expression in bacteria using recombinant DNA technology. As confirmed by Dr. DeLisa, as of the filing date of October 7, 2010, the earliest filing date to which the '345 patent is entitled ("earliest effective filing date"), POSAs would have: (a) possessed or have been pursuing a post-undergraduate degree, *e.g.*, Ph.D., in Bioengineering, Biomedical Engineering, Biomolecular Engineering, Chemical Engineering, Biotechnology, Biochemistry, Microbiology, Molecular Biology, or a comparable discipline, and (b) had at least 2-3 years of research experience relating to recombinant protein expression in bacteria. (Exh. 1006, ¶ 22).

IV. STATE OF THE ART

A. Diphtheria Toxin And CRM197

For decades, CRM197 has been used as a carrier protein in glycoconjugate vaccines for increasing the immunogenicity of saccharides. (Exh. 1006, ¶ 30; Exh. 1016, 233; Exh. 1017, 3426; Exh. 1018, 3405; Exh. 1033, 164). This includes use in prior art pneumococcal vaccines made and sold in the United States and abroad. (*See, e.g.,* Exh. 1018).

CRM197, first identified 45 years ago, is a non-toxic form of diphtheria toxin ("DTx"), a protein secreted by *Corynebacterium diphtheriae* bacteria. (Exh. 1014, 3838). CRM197 differs from DTx by one amino acid. (Exh. 1011, 4063-64, 4067-68). Both DTx and CRM197 are made of two subunits joined by disulfide bonds. (Exh. 1015, 12148; Exh. 1026, 74, Fig. 1). Well before the '345 patent's earliest effective filing date (October 7, 2010), the amino acid sequences of native DTx and CRM197 were known and used, as were polynucleotide sequences encoding these polypeptides. (Exh. 1011, 4065-66; Exh. 1050, 6592; Exh. 1055, 6855; Exh. 1006, ¶¶ 28-29).

B. Bacterial Recombinant Polypeptide Production Systems Were Well-Known And Diphtheria Toxin Expression Was Routine

For decades before the '345 patent's earliest effective filing date, recombinant DNA technology—by which DNA sequences that do not exist in nature are made and used—facilitated the expression of polypeptides of interest in bacteria. (Exh.

1061, 405-33; Exh. 1029, 5.1-5.95, 17.1-17.44; *see also* Exh. 1020, 211; Exh. 1021, 3-5); Exh. 1031, 3240; Exh. 1069, 270-79; Exh. 1070, 924-32; Exh. 1006, ¶¶ 31-39, Appendix C). By the ’345 patent’s earliest effective filing date, commonly-used undergraduate-level molecular biology textbooks described this technology. (Exh. 1037, 532; Exh. 1038, 246; Exh. 1006, ¶ 31)[4]

By the ’345 patent’s earliest effective filing date, bacterial recombinant expression systems routinely produced DTx mutants, including CRM197. (*See, e.g.,* Exh. 1032, 855; Exh. 1023, 15016; Exh. 1019, 680, 685; Exh. 1044, 1647-49; Exh. 1049, 5141, 5143; Exh. 1028, 343; Exh. 1036, 253; Exh. 1013, 8467; Exh. 1067, 370-71; Exh. 1030, 6:15-7:22; Exh. 1005, 4:64-6:3; Exh. 1006, ¶ 32).

It was common for recombinant expression of DTx mutants to involve transport of the toxin polypeptides to the bacterial periplasm, which was known to be favorable for the expression of many polypeptides. In particular, commercially

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[4] One well-known recombinant DNA approach for producing polypeptides in bacterial host cells involved the use of a collection of polynucleotides organized into a "plasmid” DNA expression vector that bacteria recognize and process. (Exh. 1037, 540-41, 546-48; Exh. 1006, ¶ 35, Fig. 1).

available polynucleotide expression vectors[5] with signal sequences capable of directing periplasmic transport of polypeptides were used to produce DTx mutants with greater than 98% identity to CRM197. (Exh. 1013, 8467; Exh. 1067, 370-71; Exh. 1005, 4:64-6:3; Exh. 1006, ¶ 33).

C. POSAs Knew The Advantages Of Transporting Polypeptides Through The Cytoplasmic Membrane To The Bacterial Periplasm

Certain bacteria, referred to as "gram negative" bacteria, *e.g.*, *Escherichia coli* and *Pseudomonas fluorescens* (Exh. 1020, 211, 217-19), contain a lipid bilayer membrane, referred to as the cytoplasmic (also, "inner" or "plasma") membrane, adjacent to the cell cytoplasm and an outer membrane (composed of lipopolysaccharide and protein) adjacent to the extracellular milieu. (Exh. 1037, 617-18). The space created between the two membranes is referred to as the "periplasm" or "periplasmic space." (*See* Exh. 1038, 247, Fig. 10.44; Fig. 1 below; Exh. 1006, ¶ 40).

[5] Terms such as "expression vector," "expression construct" and "translation vector" are used interchangeably in the literature (and herein) to refer to a polynucleotide designed to express a protein of interest. (Exh. 1006, ¶ 33 n.4). As used herein, reference to a polynucleotide "vector" or a polynucleotide "construct" refers to an expression vector, unless otherwise indicated.

Polypeptide translation begins in the cytoplasm. Long before the '345 patent, POSAs understood that polypeptides produced by a bacterial cell could be transported[6] through the cytoplasmic membrane to the periplasm. (Exh. 1038, 247, Fig. 10.44; Exh. 1006, ¶ 41). As noted below, polypeptide transport to the periplasm can occur after the polypeptide has been fully translated or while the polypeptide is still being translated.

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[6] The art uses different terms to refer to the process of transport of a polypeptide through the cytoplasmic membrane to the periplasm, including "export," "secretion," "translocation" or "expression" of the polypeptide in or to the periplasm; and to "periplasmic expression." (*See, e.g.*, Exh. 1027, 7859 ("secreted into the periplasmic space"); Exh. 1008, 2983 ("export to the periplasm"; "translocation of these proteins across the cytoplasmic membrane"); Exh. 1020, 214 ("[p]eriplasmic expression")). Thus, unless otherwise noted, these terms and similar ones will be treated interchangeably.

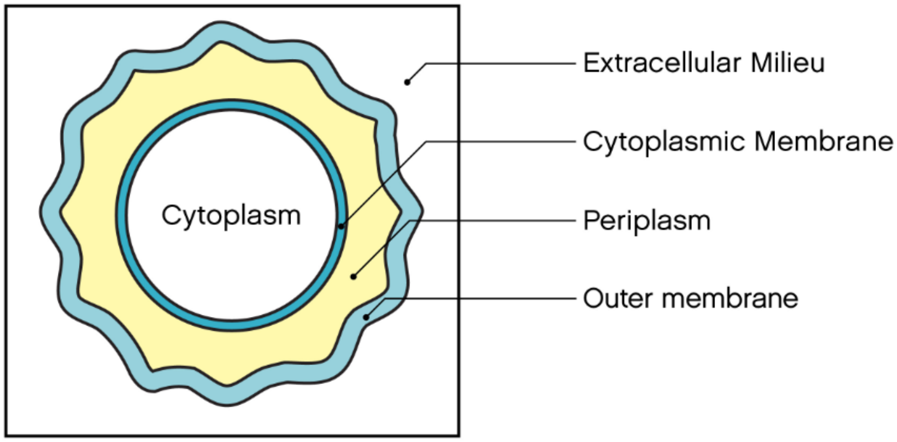

Figure 1. Representative bacterial periplasm in a gram-negative bacterium (derived from Exh. 1056, 68).

Three basic components are responsible for the transport of most polypeptides across the cytoplasmic membrane to the periplasm: 1) transport machinery of the cell in which expression occurs; 2) a signal sequence attached at the N-terminus of the protein of interest[7], and 3) exportability of the protein of interest, *i.e.*, whether the protein is intrinsically compatible with the cell's transport machinery, such that the polypeptide can be transported. (Exh. 1057, 4-5; Exh. 1064, 347; Exh. 1008, 2983-84; Exh. 1006, ¶ 42).

As the '345 patent discloses in a discussion of the prior art, POSAs knew the

[7] A polypeptide has two ends: a leading end or amino terminus ("N-terminus"), and a carboxyl terminus ("C-terminus"). (Exh. 1037, 128).

advantages of directing transport to the periplasm: (1) the oxidizing environment of the periplasm that "allows the formation of disulfide bonds" which "may help produce soluble, correctly folded proteins" (Exh. 1001, 2:39-41; *see also* Exh. 1015, 12148; Exh. 1021, 57; Exh. 1020, 215), (2) the presence of fewer proteases (enzymes that break down proteins) than the cytoplasm (Exh. 1001, 2:42-44; Exh. 1059, 1830-33), and (3) ease of polypeptide recovery (Exh. 1001, 2:45-46; Exh. 1005, 7:14-18). Moreover, it was known that periplasmic transport produced polypeptides with authentic N-termini, which is usually required for polypeptides used as human therapeutics. (Exh. 1064, 346). As a result, as of the '345 patent's earliest effective filing date, production and use of polynucleotides for "export of proteins from bacterial cytoplasm [was] widely employed." (Exh. 1020, 214; Exh. 1006, ¶ 43).

D. The Pathways That Cells Use For Polypeptide Transport Across Cytoplasmic Membranes Were Well-Known

The pathways for transporting polypeptides across the cytoplasmic membrane and into the periplasm were known before the earliest effective filing date of the '345 patent. The transport pathways have been maintained throughout evolutionary history (*i.e.,* are highly conserved) among species, including from bacteria to humans. (Exh. 1022, 1726-27; Exh. 1040, 36; Exh. 1060, 17; Exh. 1006, ¶ 44). The vast majority of polypeptides directed across the cytoplasmic membrane utilize the general secretory ("Sec") pathway (Exh. 1048, 6115), or the very similar SRP ("signal recognition particle") pathway, which is often regarded as a sub-category of the Sec pathway (Exh. 1022, 1726; Exh. 1060, 18-19; Exh. 1051, [0029]; Exh. 1006, ¶ 45).

Functionally, the main difference between the Sec and SRP pathways is that polypeptides transported via the Sec pathway are first fully translated in the cytoplasm (and, therefore, transport occurs post-translationally), while via the SRP pathway, a growing polypeptide is transported to the periplasm co-translationally, that is, while the polypeptide is still being translated. (Exh. 1057, 3, 8-9). Nonetheless, the Sec and SRP pathways feature the same basic components for protein transport across the cytoplasmic membrane discussed above—the transport machinery, a signal sequence, and an export-compatible protein of interest. Both pathways converge at the same core machinery (a complex of the SecY, SecE, and SecG proteins (collectively, "SecYEG translocon")) and require the presence of a signal sequence attached to the N-terminus of the polypeptide to be transported. (Exh. 1060, 19, Fig. 1; Exh. 1057, 3-5, 9-10; Exh. 1020, 215; Exh. 1022, 1726-27, 1741). The signal sequences used by the pathways are highly similar. (Exh. 1057, 4-5; Exh. 1008, 2988; Exh. 1006, ¶¶ 46-47).

E. The Purpose, Identity And Use Of Signal Sequences Were Well-Known

The purpose of a signal sequence is to direct polypeptides across the cytoplasmic membrane to the periplasm. (Exh. 1020, 215; Exh. 1022, 1741). When a signal sequence is attached to the N-terminus of a polypeptide intrinsically compatible with the host cell's transport machinery (*i.e.*, a protein that is "exportable"), the signal sequence directs transport of the polypeptide to the periplasm. This ability of signal sequences to direct protein transport in cells had been known for decades prior to the earliest effective filing date of the '345 patent. (*See* Exh. 1023, 15016; Exh. 1024, 4380-82; Exh. 1006, ¶¶ 48 & 50).

1. POSAs Knew of a Variety of Signal Sequences Capable of Directing Transport of Polypeptides Through the Cytoplasmic Membrane

By the time of the '345 patent's earliest effective filing date, a variety of signal sequences[8] were commonly used for transport of polypeptides into the periplasm. (Exh. 1020, 215 (listing thirteen signal sequences "in use for secretion of heterologously expressed proteins"); Exh. 1008, 2988 (demonstrating use of nine of the ten *E. coli* signal sequences recited in the '345 patent claims, to direct periplasmic transport); Exh. 1045, 7038-39; Exh. 1025, 906-08 (demonstrating the use of PelB, OmpA and synthetic CSP signal sequences, for periplasmic transport of human proteins); Exh. 1068, 1486, 1489-90 (demonstrating periplasmic transport using a PelB signal sequence encoded by the pET22b vector and various *P. fluorescens* signal sequences); Exh. 1006, ¶ 52).

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[8] The signal sequence literature uses the terms "signal sequence," "leader sequence," and "signal peptide" interchangeably.

It was known that the signal sequence and polypeptide could originate from different species, and that signal sequences from one species could be used for polypeptide transport in a different species. (*See*, *e.g.*, Exh. 1013, 8467-68; Exh. 1067, 370-71; Exh. 1005, 4:64-6:3 (*Erwinia carotovora* PelB signal sequence directs periplasmic transport of DTx mutants); Exh. 1025, 906, 911 (non-human signal sequences transport human proteins to the bacterial periplasm); Exh. 1043, 1938 (human signal sequences directed periplasmic transport of bacterial enzyme in *E. coli*); Exh. 1020, 215 (*E. carotovora* PelB signal sequence used extensively to direct periplasmic transport of diverse heterologous proteins of interest in *E. coli*); Exh. 1027, 7862 (signal sequence of subtilisin from *B. subtilis* directs periplasmic transport of recombinant proteins in *E. coli*); Exh. 1062, 854 (*Cellulomonas fimi* cellulose Cex leader (signal) sequence directs periplasmic transport of recombinant protein in *E. coli*); Exh. 1023, 15016; Exh. 1044, 1647-49 (*C. diphtheriae* DTx signal sequence directs periplasmic transport of DTx mutants in *E. coli*); Exh. 1006, ¶ 53).

2. Commercially Available Bacterial Expression Kits Were Commonly Used to Direct Transport of DTx Mutant Polypeptides to the Bacterial Periplasm

By the time of the ’345 patent’s earliest effective filing date, commercially available bacterial expression kits were readily available for directing transport of polypeptides to the periplasm. (Exh. 1021, 3, 5-24, 38, 42-43, 55-65; Exh. 1039;

Exh. 1020, 212). These kits featured polynucleotide vectors designed to allow POSAs to easily insert DNA segments encoding polypeptides of interest, as well as detailed instructions for expressing and harvesting the polypeptides. (Exh. 1021, 3-24; Exh. 1006, ¶ 54).

Novagen[9] sold polynucleotide expression vectors as part of its widely used "pET System." That system was described as "the most powerful system yet developed for the cloning and expression of recombinant proteins in *E. coli*" and "designed for convenient cloning, expression, detection and purification of target proteins." (Exh. 1021, 3; Exh. 1006, ¶ 54). The pET System included vectors specifically designed to encode signal sequences capable of directing transport of polypeptides to the periplasm. (Exh. 1021, 26-27, 38, 40, 42-43). These vectors were marketed as a "strategy to obtain active, soluble proteins . . . export[ed] into the periplasm, which is a more favorable environment for folding and disulfide bond formation." (Exh. 1021, 38; Exh. 1006, ¶ 55).

One such Novagen product was the pET22b vector, which was designed to

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[9] Novagen (now EMD Millipore) was involved in, among other things, the marketing and sale of systems, reagents and other technology designed to facilitate recombinant expression of proteins in bacteria. (Exh. 1021, 3-5).

facilitate production of polynucleotides encoding polypeptides of interest attached to a PelB signal sequence for transport to the *E. coli* bacterial periplasm. (Exh. 1021, 40, 42; Exh. 1012; Exh. 1006, ¶¶ 55-57).[10] Indeed, by the '345 patent's earliest effective filing date, the pET22b vector, with a polynucleotide encoding a PelB signal sequence placed N-terminal to a bacterial toxin, had produced mature bacterial toxins with greater than 98% sequence identity to CRM197, which were transported to the bacterial periplasm of *E. coli*. (*See* Exh. 1005, 4:64-6:3; Exh. 1006, ¶ 58).

F. POSAs Knew DTx Mutants, Including CRM197, Were Exportable To The Bacterial Periplasm

As of the '345 patent's earliest effective filing date, CRM197, and other DTx mutants were well-known exportable polypeptides, both native and non-native

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[10] Prior to the earliest effective filing date of the '345 patent the PelB signal sequence was known to be capable of directing transport of polypeptides to the bacterial periplasm, and was routinely utilized to do so. PelB signal sequence encoded by pET System vectors was known to direct polypeptide transport to the bacterial periplasm. (*See, e.g.,* Exh. 1065, 3995 (utilizing the pET20b vector); Exh. 1068, 1486 (utilizing the pET22b vector); Exh. 1066, 71 (utilizing the pET26b vector); Exh. 1006, ¶ 56).

signal sequences transported such polypeptides to bacterial periplasm during protein production. (Exh. 1005, 4:64-6:3 (periplasmic transport in *E. coli* of DTx polypeptides having greater than 98% identity to CRM197 attached to a PelB signal sequence); Exh. 1049, 5141, 5143 (periplasmic transport of CRM197 in *E. coli* with native *C. diphtheriae* signal sequence); Exh. 1023, 15016 (periplasmic transport in *E. coli* of a DTx fragment with native *C. diphtheriae* signal sequence); Exh. 1007, [0178], [0182], Fig. 9 (secretion in *E. coli* of a DTx mutant fusion protein with *E. carotovora*'s PelB signal sequence)). Collier-1 is illustrative, demonstrating periplasmic transport in *E. coli* of a DTx mutant polypeptide in which the host cell, signal sequence, and DTx mutant were each from a different species. (Exh. 1005, 4:64-6:3; Exh. 1006, ¶ 63).

V. THE '345 PATENT

The '345 patent issued on August 23, 2016 and is assigned on its face to GlaxoSmithKline Biologicals S.A. (Exh. 1001, IPR1).

In general, the '345 patent relates to polynucleotides encoding a signal sequence and a bacterial toxin, for the production of polypeptides in the periplasm of bacteria.

Claim 1 of the '345 patent, one of two independent claims, is directed to a polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion:

> 1. A polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion wherein:

(a) the 3’ toxin portion encodes a mature bacterial toxin polypeptide having an amino acid sequence at least 90% identical to SEQ ID NO: 32; and

(b) the 5’ signal sequence portion encodes a polypeptide having an amino acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell, and wherein the 5’ signal sequence is not derived from *C. diphtheriae*.

(Exh. 1001, 49:54-64). SEQ ID NO: 32 corresponds to the amino acid sequence of mature CRM197. (*Id.*, Fig, 9E).

Claims depending from claim 1 recite that the 3’ toxin portion encodes: a polypeptide having the amino acid sequence of SEQ ID NO: 32 (claim 2); CRM197 itself (claim 18); or a polypeptide having at least 95% sequence identity to SEQ ID NO: 32 (claim 19). Other claims that depend from claim 1 recite that the 5’ portion encodes specific signal sequences (claims 4-5), that the encoded polypeptide comprises specific (but known) signal sequences plus the first 30 amino acids of CRM197 (claim 20), or that the 5’ signal sequence portion is directly 5’ of the 3’ toxin portion (claim 21).

Independent claim 6 combines the elements of claims 1 and 4. Claims depending from claim 6 recite that the 3’ toxin portion encodes: a polypeptide having the amino acid sequence of SEQ ID NO: 32 (claim 14), CRM197 itself (claim 12), or a polypeptide having at least 95% sequence identity to SEQ ID NO: 32 (claim

13). Likewise, other claims that depend from claim 6 recite that the 5’ portion encodes specific (but known) signal sequences (claims 7-11), that the encoded polypeptide comprises specific (but known) signal sequences plus the first 30 amino acids of CRM197 (claim 16), or that the 5’ signal sequence portion is directly 5’ of the 3’ toxin portion (claim 17).

The ’345 patent makes clear that its examples merely combined prior art elements to achieve predictable results. The patent describes using “standard molecular biology techniques” to combine signal sequences from a public database to express a decades-old “target gene” in *E. coli*. (*Id*., 19:63-67).

Although the ’345 patent refers to “low protein abundance” and a search for ways to “increase expression” (*id*., 2:7-25), significantly, none of the claims of the ’345 patent require that the polynucleotide achieve any particular yield. Nor does the patent describe any novel sequences that are superior to those in the prior art. Finally, the patent does not include any evidence of unexpected results.

VI. CLAIM CONSTRUCTION

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable construction (“BRC”) in light of the specification of the ’345 patent.

A. "encodes a mature bacterial toxin polypeptide"

The claim term "encodes a mature bacterial toxin polypeptide" should be construed to mean "***contains a polynucleotide that, when translated,[11] yields a bacterial toxin polypeptide lacking a signal sequence***." This construction is the plain and ordinary meaning of the term and is supported by the intrinsic record.

POSAs at the time of the '345 patent's earliest effective filing date would have understood that a polynucleotide "encoding" a particular protein or polypeptide means a polynucleotide sequence that, when translated, yields that particular protein sequence. (Exh. 1037, 550-51). Likewise, POSAs would have understood that "mature" polypeptides do not include a signal sequence. (Exh. 1022, 1727; Exh. 1006, ¶ 92).

The intrinsic evidence is consistent with the plain and ordinary meaning of "mature bacterial toxin polypeptide." The specification describes the creation of a plasmid containing a "mature CRM197 sequence (SEQ ID NO:31)" which "contains no signal sequence." (Exh. 1001, 21:8-10). Figure 2 refers to "mature CRM197" and specifies that this polypeptide contains "no signal sequence." (*Id.*, Fig. 2). The specification also states that "the process for making the bacterial toxin involves

[11] "Translation" is the process by which a cell expresses a polypeptide based on the coding sequence of a polynucleotide. (Exh. 1006, ¶ 37, Appendix C, ¶ 9).

removal of a signal peptide from the bacterial toxin within the bacterial host cell to obtain a mature bacterial toxin." (*Id.*, 16:10-13; Exh. 1006, ¶ 93).

The prosecution history further confirms that a "mature" polypeptide is one lacking a signal sequence. During prosecution, in order to overcome a prior art reference that disclosed a DTx polypeptide with a signal sequence, Patent Owner ("PO") amended the claim language to add the term "mature bacterial toxin." (Exh. 1002, IPR522-23). PO stated that "'[m]ature' refers to a diphtheria toxin polypeptide lacking the signal sequence, *see* e.g. paragraphs 0153 and 0204 of the present specification." (*Id.*, IPR527; Exh. 1006, ¶ 94).[12]

Consequently, the term "encodes a mature bacterial toxin polypeptide" should be construed to mean "contains a polynucleotide that, when translated, yields a bacterial toxin polypeptide lacking a signal sequence." (Exh. 1006, ¶ 95).

B. "an amino acid sequence at least 90% *identical to*" or "at least 95% sequence *identity to*"

The claim term "an amino acid sequence at least 90% identical to" should be construed to mean "an amino acid sequence with at least 90% identity to a reference

[12] These paragraph numbers refer to the published application that issued as the '345 patent and correspond to the disclosures regarding mature toxins in the '345 patent specification discussed above. (Exh. 1001, 16:10-16, 21:4-10; Exh. 1034, [0153], [0204]).

sequence, as determined by known methods." Likewise, the term "at least 95% sequence identity to" should be construed to mean "a polypeptide with at least 95% sequence identity to a reference sequence as determined by known methods." (Exh. 1006, ¶ 96).

The '345 patent does not define the term "an amino acid sequence at least 90% *identical to*" or "at least 95% sequence *identity to*" a reference sequence, however the intrinsic evidence demonstrates that PO used the terms "identical to" and "sequence identity" interchangeably. Independent claim 1 is directed to a polynucleotide encoding, *inter alia*, an amino acid sequence "at least 90% ***identical to*** SEQ ID NO: 32," and claim 19, which depends from claim 1, is directed to a polynucleotide "having at least 95% sequence ***identity to*** SEQ ID NO: 32." (Exh. 1001, 49:56-58, 52:36-38 (emphases added)). This relationship exists between independent claim 6 ("90% ***identical to*** SEQ ID NO: 32") and its dependent claim 13 ("95% sequence ***identity to*** SEQ ID NO: 32"). (*Id.*, 51:15-17, 52:22-24 (emphases added); Exh. 1006, ¶ 97).

The '345 patent describes standard methods for determining an amino acid sequence's "identity" to a reference sequence. (Exh. 1001, 6:15-48). The specification's disclosure regarding sequence "identity" makes clear that "'[i]dentity' can be readily calculated by known methods," identity is "determined by the match between strings of such sequences," "[m]ethods to determine identity are designed to give the largest match between the sequences tested," and that such methods "are codified in publicly available computer programs" such as BLAST.[13] (*Id*., 6:18-47; Exh. 1006, ¶ 98).

In view of these disclosures, the claim term "an amino acid sequence at least 90% identical to" should be construed to mean "an amino acid sequence with at least 90% identity to a reference sequence, as determined by known methods." Likewise, the term "at least 95% sequence identity to" should be construed to mean "a polypeptide with at least 95% sequence identity to a reference sequence as determined by known methods." (Exh. 1006, ¶ 99).

C. "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm"

Claims 1 and 6 recite that the 5' signal sequence portion encodes a polypeptide having an amino acid sequence "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell." (Exh. 1001, 49:59-62, 51:18-21). This term is not defined in the specification of the '345 patent and should be given its plain and ordinary meaning in light of the specification.[14]

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[13] *See, e.g.*, https://blast.ncbi.nlm.nih.gov/Blast.cgi.

[14] The inventor must provide a clear indication of their intent to act as their

The plain and ordinary meaning of the "capable of" portion of this term is well-known. *See Ricoh Americas Corp. v. MPHJ Tech. Invs., LLC*, No. IPR2014-00538, Paper 8 at 9-10 (P.T.A.B. Aug. 25, 2014); (*see also* Exh. 1047, 207 ("[h]aving capacity or ability . . .[; h]aving the ability required for a specific task or accomplishment"); Exh. 1035, 168 ("having attributes . . . required for performance or accomplishment . . .[;] having traits conducive to or features permitting"); Exh. 1006, ¶ 101). The remainder of this term is directed to basic biological terminology well-known to POSAs. Accordingly, no construction of this term is required. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) ("[i]n some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges"); *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997); *Syntheon, LLC v. Covidien AG*, No. 16-10244-ADB, 2017 WL 4225994, at *9 (D. Mass. Sept. 22, 2017).

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own lexicographer, which they may do by placing quotation marks around the terms in question. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The applicants for the '345 patent clearly identified the terms they wished to define in this manner. (Exh. 1001, 7:5-25). Their decision not to define the "capable of" term (*e.g.*, not to put it in quotations) manifests their intent to give this term its well understood ordinary meaning, and not to act as their own lexicographers.

The Board should reject any attempt by PO to improperly incorporate limitations from the specification, such as a particular amount of transport to the periplasm, and/or a specific type of bacteria. PO might point to a passage of the specification where it states that "[a] signal sequence is capable of directing an expressed protein to the periplasm if, when it is attached to a polypeptide of interest, during translation of the polypeptide in a gram negative bacteria, more of said polypeptide is found in the periplasm of a gram negative bacteria than in the absence of the signal sequence." (Exh. 1001, 7:33-39). But this statement does not meet the exacting standard for disavowal of claim scope. The inclusion of a sentence identifying ***one example*** of "a signal sequence [] capable of directing an expressed protein to the periplasm" that relates to a particular amount of transport to the periplasm and/or expression in a specific type of bacteria does not mean that it "limits all subsequent claims." *Unwired Planet, LLC v. Apple Inc.,* 829 F.3d 1353, 1358 (Fed. Cir. 2016); *see Thorner v. Sony Computer Entm't Am. LLC,* 669 F.3d 1362, 1366 (Fed. Cir. 2012). The specification "is not a substitute for, nor can it be used to rewrite, the chosen claim language." *SuperGuide Corp. v. DirecTV Enters., Inc.,* 358 F.3d 870, 875 (Fed. Cir. 2004).

There is no clear intention in the specification to limit the scope of the claims to that embodiment. Indeed, the Federal Circuit has emphasized that "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" *Liebel-Flarsheim Co. v. Medrad, Inc.,* 358 F.3d 898, 906 (Fed. Cir. 2004). And even though the inventors plainly understood how to describe such an embodiment in the specification (Exh. 1001, 7:33-38), the claims notably do not limit the claimed compositions to expression in a particular type of bacteria, or require any particular amount of transport to the periplasm. Accordingly, well established principles of patent law prohibit reading those (or any other) limitations from the specification into the claims.

D. "wherein the 5' signal sequence is not derived from *C. diphtheriae*"

Claims 1 and 6 recite "wherein the 5' signal sequence is not derived from *C. diphtheriae*." (*Id.*, 49:63-64, 51:22-23). This term should be construed to mean "wherein the signal sequence of a polypeptide is different in amino acid sequence to the signal sequence of the mature bacterial toxin polypeptide found in native (not recombinant) *C. diphtheriae*." (Exh. 1006, ¶ 102).

This construction is supported by the claim language and specification. POSAs would understand the "not derived from *C. diphtheriae*" claim language, based on the specification, to capture signal sequences that are different than found in native (not recombinant) *C. diphtheriae*. While this exact claim term is not defined in the specification, a similar term "polypeptide **not derived from** *C.*

diphtheriae" is defined as "a polypeptide **which is different in sequence** to a polypeptide **found in native (not recombinant)** *C. diphtheriae*." (Exh. 1001, 7:22-24 (emphases added); Exh. 1006, ¶ 103). Petitioner has adopted the relevant portions of this definition into its proposed construction of this term. Accordingly, the specification supports Petitioner's proposed construction. *See Phillips*, 415 F.3d at 1315; *see also Vitronics*, 90 F.3d at 1582.

Although PO argued during prosecution that "not derived from *C. diphtheriae*" excluded "***modified*** native *C. diphtheriae* signal sequence[s]," that argument is irrelevant to the clear guidance supplied by the specification. (Exh. 1002, IPR527 (emphasis added)). Because the prosecution history "often lacks the clarity of the specification and thus is less useful for claim construction purposes," *Phillips*, 415 F.3d at 1317, the claim term should be construed in accordance with the definitions in the specification. "[W]hen the specification and prosecution history appear in conflict, any ambiguity must be resolved in favor of the specification and claims. . . ." *Lydall Thermal/Acoustical, Inc. v. Fed. Mogul Corp.*, 566 F. Supp. 2d 602, 614 (E.D. Mich. 2008), *aff'd*, 344 F. App'x 607 (Fed. Cir. 2009). For these reasons, this term should be construed in accordance with the claim language and the specification to mean "wherein the signal sequence of a polypeptide is different in amino acid sequence to the signal sequence of the mature bacterial toxin polypeptide found in native (not recombinant) *C. diphtheriae*."

The remaining terms of the challenged claims are explicitly defined by the specification or have a well understood ordinary meaning to POSAs and require no further construction for the purposes of this Petition.

VII. THE ’345 PATENT IS NOT ENTITLED TO THE OCTOBER 8, 2009 FILING DATE OF GB-647

The ’345 patent issued from a national stage application of PCT-047 (Exh. 1003), which claims benefit to GB-647 (Exh. 1004), filed October 8, 2009. For the ’345 patent to be entitled to GB-647’s filing date, GB-647 must provide sufficient written description under pre-AIA 35 U.S.C. § 112 for the ’345 patent claims. *In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995). GB-647 must itself describe an invention in sufficient detail that POSAs can clearly and immediately conclude that the patent applicant was in possession of the claimed subject matter as of GB-647’s filing date. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997); *Ex parte Shang*, No. 2008-4272, 2008 WL 4384078, at *3 (B.P.A.I. Sept. 25, 2008).

GB-647 fails to provide written description for at least two claim elements (1) “wherein the 5’ signal sequence is not derived from *C. diphtheriae*” (*i.e.*, the “not-derived-from” limitation) and (2) “amino acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm” (*i.e.*, the “capable of directing transport” limitation). Accordingly, the ’345 patent claims are not entitled to GB-647’s October 8, 2009 filing date.

A. GB-647 Does Not Provide Written Description For The "Not-Derived-From" Limitation

Both independent claims recite the "not-derived-from" limitation. (Exh. 1001, claims 1 & 6). This limitation first appeared in claim 2 of PCT-047. (Exh. 1003, 29). In the Summary of the Invention, PCT-047 disclosed, for the first time, that "[i]n a second aspect of the invention, there is provided a polynucleotide . . . wherein the 5' signal sequence is not derived from *C. diphtheriae.*" (Exh. 1003, 2:42-46). Further, PCT-047 disclosed that "[i]n one embodiment the 5' signal sequence is not the tox signal sequence from *Corynebacterium diphtheriae*." (Exh. 1003, 8:18-19). By contrast, GB-647 did not contain any such disclosures.

PCT-047 also introduced a definition for a similar claim term, "polypeptide not derived from *C. diphtheriae*," which definition was not found in GB-647. As discussed above, this term is defined as "a polypeptide which is different in sequence to a polypeptide found in native (not recombinant) *C. diphtheriae*." In view of this definition and the claim language, the "not-derived-from" limitation means "wherein the signal sequence of a polypeptide is different in amino acid sequence to the signal sequence of the mature bacterial toxin polypeptide found in native (not recombinant) *C. diphtheriae*."

Absent this definition in the '345 patent and PCT-047, POSAs would have understood the "not-derived-from" limitation in the '345 patent and PCT-047 to exclude polynucleotides encoding *C. diphtheriae* mutant signal sequences from the scope of the claims, regardless of whether that mutant signal sequence is different than that of the mature bacterial toxin polypeptide found in native (not recombinant) *C. diphtheriae*. In contrast, POSAs would understand the "not-derived-from" limitation in the '345 patent and PCT-047, as defined therein, as including *C. diphtheriae* mutant signal sequences within the scope of the claims because they have a different amino acid sequence from that of the mature bacterial toxin polypeptide found in native (not recombinant) *C. diphtheriae*. (Exh. 1006, ¶¶ 108-109).

GB-647 discloses that in one aspect of the invention, the polynucleotide comprises a 5' signal sequence portion that encodes a heterologous polypeptide. (Exh. 1004, IPR7). This application defines the term "heterologous peptide" as a peptide which is not native to the cell type in which it is expressed. (*Id*., IPR14). GB-647 also discloses that the bacterial host can be *E. coli* as well as other species other than *C. diphtheriae*. (*Id*., IPR19). This disclosure in GB-647 allows for both native and mutant *C. diphtheriae* signal sequences to be used in non-*C. diphtheriae* hosts. Thus, in view of this disclosure, without the definition for the "not derived from limitation," POSAs would not have appreciated, based on GB-647, that the claimed signal sequences exclude solely ones found in native *C. diphtheriae* and that *C. diphtheriae* mutant signal sequences were not excluded. (Exh. 1006, ¶ 110).

Therefore, GB-647 failed to disclose that the inventors were in possession of the claimed polynucleotide.

PO's statements during prosecution confirm that the "not-derived-from" limitation is not supported by GB-647. This limitation was added to then-pending independent claim 76 (issued claim 1) to overcome an anticipation rejection. (Exh. 1002, IPR527). In connection with the amendment, PO stated that "[t]his amendment is supported in the specification and claims as filed, e.g., at paragraph 0020" (*id.*), referring to portions of the specification which <u>did not appear in GB-647</u>. (*See* Exh. 1003, 2:42-50; Exh. 1034, [0020]-[0022]). This confirmed the absence of any support for this limitation in GB-647. Notably, the "not-derived-from" limitation was added to claim 82 (issued claim 6) in a subsequent amendment. (Exh. 1002, IPR571). As a result, each claim of the '345 patent includes the "not-derived-from" limitation, and, consequently, all the claims are not entitled to GB-647's October 8, 2009 filing date.

GB-647 discloses certain signal sequences that can be encoded by the 5' portion. (Exh. 1004, IPR29 (Table 2)). Unlike the '345 patent and PCT-047, GB-647 does not indicate the origin or bacterial species from which these signal sequences originate. (Exh. 1001, Table 2; Exh. 1003, 19 (Table 2)). Table 2 of each of the '345 patent and PCT-047 shows that the signal sequences originate from four bacterial species, none of which are *C. diphtheriae* (*i.e.*, *E. coli*, *S. pneumoniae*, *Group B Streptococcus* and *N. meningitides*).[15] However, disclosure in GB-647 of signal sequences that do not originate from *C. diphtheriae* does not provide sufficient information regarding the metes and bounds of the "not-derived-from" limitation. (Exh. 1006, ¶ 111).

Specifically, even assuming that the signal sequences disclosed in GB-647 happen to be "not derived from *C. diphtheriae*," such disclosure does not provide sufficient support for this limitation. *Shang*, 2008 WL 4384078, at *5-6 (disclosure of several examples satisfying the claim limitation did not provide sufficient written description); *In re Lukach*, 442 F.2d 967, 969-70 (C.C.P.A. May 27, 1971) (same). This is particularly the case since GB-647 discloses and claims embodiments in which the signal sequences can originate from any bacterial species (*i.e.*, signal sequences do not have to be different from ones originating from any particular bacterial species). (Exh. 1004, IPR7-8, IPR17, IPR40).

Even assuming that disclosure of GB-647's signal sequences teaches that the claimed signal sequence do not originate from *C. diphtheriae*, such teaching would not have informed POSAs as to the scope of this claim term. POSAs would not have

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[15] That the species of these signal sequences were not indicated in GB-647 and only first disclosed in PCT-047 shows that PO did not consider the origin of the signal sequences to be important when GB-647 was filed.

understood that the claimed signal sequences exclude solely ones that are the same as found in native *C. diphtheriae* and do not exclude *C. diphtheriae* mutant signal sequences. Thus POSAs would not have concluded that PO was in possession of the claimed polynucleotides comprising a 5' portion encoding a signal sequence having the claimed feature. (Exh. 1006, ¶ 112).

Accordingly, GB-647 does not disclose the "not-derived-from" limitation and the '345 patent claims are not entitled to GB-647's filing date.

B. GB-647 Does Not Provide Written Description For The "Capable Of Directing Transport" Limitation

Both independent claims of the '345 patent recite that "the 5' signal sequence portion encodes a polypeptide having an amino acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm." (Exh. 1001, claims 1 & 6). GB-647 does not support the '345 patent claims because that application demonstrates that the applicants did not appreciate the full scope of what they eventually claimed in the '345 patent. PO's interpretation of data from the examples of the '345 patent (which was not disclosed in GB-647) significantly expanded the scope of signal sequences "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm." This change demonstrates that PO was not in possession of the full scope of the claimed subject matter at the filing date of GB-647. Accordingly, GB-647 lacks written description for the '345 patent claims.

Examples 1, 4 and 5 in the ’345 patent describe the same experiments as Examples 1, 4 and 5 in GB-647. (Exh. 1001, 19:58-20:54, 21:50-22:46; Exh. 1004, IPR29-32). However, the ’345 patent and its description of these examples significantly expanded the scope of signal sequences “capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm.” Table 1 of GB-647 teaches that the signal sequences OmpA, FocC, YraI, and PhtE exhibited “no expression visible on the Western blot,” as indicated by the “-” symbol. (Exh. 1004, IPR10 (Table 1)). GB-647 reiterates in Example 5 that “no expression was seen” for constructs with these signal sequences. (*Id.*, IPR32). GB-647 therefore described these signal sequences as not being “capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm.” (Exh. 1006, ¶ 115).

In contrast, the disclosure reporting “no expression” from the OmpA, FocC, YraI, and PhtE signal sequences was deleted from the ’345 patent. Specifically, the right-most column with the marks in Table 1 of GB-647 was omitted from Table 1 of the ’345 patent. (*Compare* Exh. 1001, 4:22-40 *with* Exh. 1004, IPR9-10). The statement in Example 5 of GB-647 that there was no expression for these four signal sequences was also removed from Example 5 in the ’345 patent. (Exh. 1001, 22:20-46; Exh. 1006, ¶¶ 115-116).

PO added claims to the ’345 patent reciting that these four signal sequences (identified by SEQ ID NOs: 6, 14, 18, and 2, respectively) are “capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm." (*Compare* Exh. 1001, 50:59-63 *with* Exh. 1004, IPR9-10 (Table 1)). Thus, the '345 patent expanded the scope of signal sequences falling within the scope of the claims, compared to those described in GB-647. (Exh. 1006, ¶ 116). These changes confirm that PO was not in possession of the full scope of the claimed subject matter of the '345 patent at GB-647's filing date. Thus, the '345 patent claims are not entitled to the October 8, 2009 filing date of GB-647 under Section 112, first paragraph.

VIII. GROUNDS FOR INSTITUTION

A. Ground I: Claims 1-2, 18-19 And 21 Of The '345 Patent Are Anticipated By Retallack

Retallack is specifically directed to making CRM197 and teaches "a nucleotide sequence encoding a CRM197 protein fused to a secretion signal that directs transfer of the CRM197 protein to the periplasm." (Exh. 1009, [0006], claims 1 & 4; Exh. 1071, IPR12 ([0005]), claims 1 & 4)). Retallack teaches periplasmic transport in *Pseudomonas* bacteria and that the host cell can also be *E. coli*. (Exh. 1009, [0047]; Exh. 1071, IPR22 ([0045])). Retallack discloses each and every element of the '345 patent claims 1-2, 18-19, and 21. (Exh. 1006, ¶ 117).

1. Effective Reference Date of Retallack

As explained above, the '345 patent is not entitled to the October 8, 2009 filing date of GB-647. The next earliest filing date that the '345 patent claims is the October 7, 2010 filing date of PCT-047. Retallack, which was not considered by the

Examiner during prosecution, is a WIPO publication of PCT Application No. PCT/US2010/030573 (Exh. 1009). This PCT application was filed April 9, 2010[16], designated the United States, and was published in English. (Exh. 1009, IPR1). Therefore, Retallack is prior art under pre-AIA Section 102(e) as of at least the April 9, 2010 filing date. MPEP 706.02(f)(1).

Retallack claims benefit to U.S. Provisional Patent Application No. 61/319,152 ("Retallack-Provisional"), which was filed March 30, 2010. (Exh. 1071, IPR1). Retallack is entitled to this provisional filing date if: (1) the material being relied upon in Retallack is carried over from the Retallack-Provisional to Retallack, and (2) the Retallack-Provisional provides support for the claims in Retallack, in compliance with Section 112, paragraph 1. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1382 (Fed. Cir. 2015); *Cisco Sys., Inc. v. Capella Photonics, Inc.*, No. IPR2014-01166, Paper 44, at 16-21 (P.T.A.B. Jan. 28, 2016) (Section 102(e) reference entitled to provisional filing date).

Each of Retallack-Provisional and Retallack discloses the subject matter of the '345 patent claims. In fact, they are virtually identical. (*Compare* Exh. 1071 *with* Exh. 1009). The Retallack-Provisional provides the required Section 112,

[16] This is the relevant date for determining whether Retallack is pre-AIA prior art. MPEP 706.02(f)(1) (9th ed., Rev. 08.2017, Jan. 2018).

paragraph 1 support for Retallack's claims. The Retallack-Provisional includes the same 16 method claims as Retallack. (*Compare* Exh. 1009, 31-33 *with* Exh. 1071, IPR44-46). The Retallack-Provisional describes the methods claimed in Retallack and provides information, including examples, on how to practice them. (*See, e.g.*, Exh. 1071, IPR39-43). Accordingly, Retallack is entitled to the filing date of the Retallack-Provisional as its effective reference date.

2. Claim 1 Is Anticipated

a. "A polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion"

Retallack teaches the use of a polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion. Specifically, Retallack describes polynucleotides, each of which comprises a 3' toxin portion encoding CRM197 and a 5' signal sequence portion encoding one of ten different *P. fluorescens* "secretion leaders." (Exh. 1009, [0036], [0080], Table 6; Exh. 1071, IPR40 (Table 6), IPR19 ([0034]), IPR40 ([0078]))[17]. Retallack uses "secretion signal" and "secretion leader" interchangeably, stating that such sequences are used to transfer, or target, CRM197 to the periplasm. (Exh. 1009, [0006], [0080]; Exh. 1071, IPR12 ([0005]), IPR40 ([0078])). As discussed above, translation of a polynucleotide occurs in the 5' to 3'

[17] To show that both Retallack and the Retallack-Provisional disclose the subject matter of the challenged claims, citations to both are provided.

direction. Therefore, in teaching the N-terminal nature of secretion leaders attached to CRM197 (*see, e.g.*, Exh. 1009, [0036]), Retallack teaches that the signal sequence portion of the polynucleotide is situated 5' relative to the 3' toxin portion of the polynucleotide that encodes CRM197. Accordingly, Retallack discloses this limitation. (Exh. 1006, ¶¶ 118-119).

b. "wherein (a) the 3' toxin portion encodes a mature bacterial toxin polypeptide"

The claim term "encodes a mature bacterial toxin polypeptide" means "contains a polynucleotide that, when translated, yields a bacterial toxin polypeptide lacking a signal sequence."

Retallack describes the preparation of polynucleotides with a 3' portion that encodes the CRM197 amino acid sequence. Retallack teaches that its "Figure 1 shows the amino acid and DNA sequences of the expressed synthetic CRM197 gene." (Exh. 1009, [0079]; Exh. 1071, IPR40 ([0077])). The amino acid sequence in Figure 1 of Retallack is 100% identical to SEQ ID NO: 32, the amino acid sequence of mature CRM197, that is, CRM197 which lacks a signal sequence. (Exh. 1001, Fig. 9E). Thus, Retallack teaches this limitation. (Exh. 1006, ¶¶ 120-122).

c. "having an amino acid sequence at least 90% identical to SEQ ID NO: 32"

The amino acid sequence in Figure 1 of Retallack is 100% identical to SEQ ID NO: 32. (Exh. 1001, Fig. 9E, Sequence Listing; Exh. 1009, Fig. 1; Exh. 1071, IPR48 (Fig. 1)). Therefore, Retallack teaches this limitation. (Exh. 1006, ¶¶ 123-124).

d. "and (b) the 5' signal sequence portion encodes a polypeptide having an amino acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell"

Retallack teaches "a nucleotide sequence encoding a CRM197 protein fused to a secretion signal that directs transfer of the CRM197 protein to the periplasm." (Exh. 1009, [0006], claims 1 & 4; Exh. 1071, IPR12 ([0005]), IPR44 (claims 1 & 4)). Retallack also provides a working example that generates a number of polynucleotides each of which encodes CRM197 fused to one of ten different *P. fluorescens* signal sequences, "included to target the protein to the periplasm . . . for recovery in the properly folded and active form." (Exh. 1009, [0080]; Exh. 1071, IPR40 ([0078]); Exh. 1006, ¶ 125).

Retallack concluded that the disclosed signal sequences directed the transport of CRM197 into the bacterial periplasm. Upon testing the polypeptides containing the ten secretion leaders fused to the recombinant CRM197 protein, (Exh. 1009, [0081]; Exh. 1071, IPR40 ([0079])), "*P. fluorescens*-expressed CRM197 migrated as a single band at ~58 kDa on SDS-CGE." (Exh. 1009, [0018]; Exh. 1071, IPR14-15 ([0017])). Thus, Retallack teaches a 5' signal sequence portion capable of directing transport of a bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell. Accordingly, Retallack discloses this limitation. (Exh. 1006, ¶¶ 126-127).

e. "and wherein the 5' signal sequence is not derived from *C. diphtheriae*"

This claim limitation requires that the 5' signal sequence is different in sequence from the signal sequence found in native (not recombinant) *C. diphtheriae*. Retallack teaches, "[p]lasmids carrying the codon-optimized CRM197 sequence, fused to ten *P. fluorescens* secretion leaders as shown in Table 6." (Exh. 1009, [0080]; Exh. 1071, IPR40 ([0078])). These signal sequences are native to *P. fluorescens,* not *C. diphtheriae*.[18] (Exh. 1009, [0080], Table 6; Exh. 1071, IPR18-

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[18] This is consistent with PO's statements during prosecution. In arguing for the patentability of claims reciting the specific signal sequences found at Table 2 of the '345 patent (and variants and fragments thereof), which identifies the signal sequences by bacterial origin (*S. pneumoniae*, *E. coli*, etc.), PO stated "these claims recite signal sequences that are not derived from *C diphtheriae*." (Exh. 1002, IPR527). During prosecution of the '345 patent's corresponding European application, PO made statements consistent with those made during the U.S. prosecution. Specifically, in distinguishing the prior art from claims reciting the FlgI signal sequence (SEQ ID NO: 24), which Table 2 of the '345 patent identifies as

19 ([0031])). The CupA2 signal sequence encoded by the Retallack polynucleotide constructs is not found in *C. diphtheriae*. Therefore, Retallack teaches this limitation. (Exh. 1006, ¶¶ 128-129).

Thus, Retallack discloses each and every limitation of claim 1 and anticipates claim 1.

3. Claim 2 Is Anticipated

Claim 2 recites that "the 3' toxin portion encodes a polypeptide having the amino acid sequence of SEQ ID NO: 32." (Exh. 1001, 49:65-67). SEQ ID NO. 32 of the '345 patent recites the amino acid sequence of CRM197. (*Id.*, Fig. 9E). Retallack teaches polynucleotides having a 3' toxin portion that encodes CRM197: "a nucleotide sequence encoding a CRM197 protein fused to a secretion signal that directs transfer of the CRM197 protein to the periplasm." (Exh. 1009, [0006]; Exh. 1071, IPR12 ([0005])). Retallack further teaches that "[f]igure 1 shows the amino acid and DNA sequences of the expressed synthetic CRM197 gene" and Retallack provides a working example that prepares a polynucleotide having a 3' toxin portion

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originating from *E. coli*, PO stated that the FlgI signal sequence "is not derived from *C. diptheria* . . . . Instead it is derived from *E.coli* as shown in Table 2 of Example 1." (Exh. 1063, IPR6; Exh. 1073).

encoding this amino acid sequence. (Exh. 1009, [0079], [0080]; Exh. 1071, IPR40 ([0077])). The amino acid sequence in Figure 1 of Retallack is 100% identical to SEQ ID NO: 32. Therefore, Retallack teaches this limitation and anticipates claim 2. (Exh. 1006, ¶¶ 130-132).

4. Claim 18 Is Anticipated

Claim 18 recites that "the 3' toxin portion encodes CRM197." (Exh. 1001, 52:34-35). Retallack teaches "a nucleotide sequence encoding a CRM197 protein fused to a secretion signal that directs transfer of the CRM197 protein to the periplasm." (Exh. 1009, [0006]; Exh. 1071, IPR12 ([0005])). The CRM197 encoding portion is at the 3' end. (Exh. 1009, [0036], [0080]; Exh. 1071, IPR19 ([0034]), IPR40 ([0078])). Thus, Retallack teaches this limitation and anticipates claim 18. (Exh. 1006, ¶¶ 133-134).

5. Claim 19 Is Anticipated

Claim 19 recites that "the 3' toxin portion encodes a polypeptide having at least 95% sequence identity to SEQ ID NO: 32." (Exh. 1001, 52:36-38). As discussed above, Retallack teaches a 3' toxin portion that encodes a bacterial toxin that is 100% identical to SEQ ID NO: 32 of the '345 patent. Therefore, Retallack anticipates claim 19. (Exh. 1006, ¶ 135).

6. Claim 21 Is Anticipated

Claim 21 further recites, "wherein the 5' signal sequence portion is directly 5' of the 3' toxin portion." (Exh. 1001, 52:41-42). Retallack discloses this claim limitation. Retallack teaches a polynucleotide in which the leader or signal sequence coding portion is 5' relative to the 3' portion encoding CRM197. (Exh. 1009, [0080]; Exh. 1071, IPR40 ([0078])). Retallack teaches that when producing native CRM197 in *C. diphtheriae*, a signal sequence is used, which is then cleaved, "leaving an amino terminal sequence of GADD." (Exh. 1009, [0036]; Exh. 1071, IPR19 ([0034])). Retallack further teaches designing polynucleotides, having a 5' signal sequence portion and a 3' portion encoding CRM197, for targeting the CRM197 to the periplasm to "preserve the natural amino terminus of CRM197 following expression." (*Id.*). This natural amino terminus, (*i.e.*, GADD), is the same as that of mature CRM197. (Exh. 1001, Fig. 9E; Exh. 1009, [0036], Fig. 1A; Exh. 1071, IPR19 ([0034]), IPR48 (Fig. 1A)). Thus, Retallack's teaching regarding preserving the natural amino terminus following expression shows that what is immediately 3' of the 5' signal sequence portion is the part of the polynucleotide that encodes mature CRM197. Therefore, Retallack teaches polynucleotides in which the 5' signal sequence portion is directly attached to the 3' CRM197 toxin portion. Accordingly, Retallack anticipates claim 21. (Exh. 1006, ¶¶ 136-138).

B. Ground II: Claims 4-14, 16-17 And 20 Would Have Been Obvious Over Retallack And Huber

Claims 4-14, 16-17 and 20 recite polynucleotides comprising a 5' signal sequence portion that encodes one of the following specifically-recited signal sequences, each of which were well-known as of the '345 patent's earliest effective filing date: PhtE (2), SipA (4), OmpA (6), NspA (8), TorT (10), SfmC (12), FocC (14), CcmH (16), YraI (18), TolB (20), NikA (22), FlgI (24), and DsbA (26). (SEQ ID NOs. in parentheses; *see*, *e.g.*, Exh 1001, claims 4, 6, 8, 12-14 & 17). Claim 10 recites specific nucleic acid sequences encoding these signal sequences. The 5' signal sequence in these claims can be any one of the recited signal sequences, except in claims 5, 7, and 9, which recite SEQ ID NO. 24 for the FlgI signal sequence, variants or fragments, and claim 11, which recites a specific FlgI nucleic acid sequence. Finally, claims 16 and 20 recite polynucleotides of claims 6 and 1, respectively, that encode "a polypeptide comprising any one of SEQ ID NOs: 33-45," which SEQ ID NOs correspond to the specifically-disclosed 5' signal sequences noted above plus the first 30 amino acids of CRM197. (Exh. 1001, 50:55-58, 51:13-26, 52:30-31, 52:39-40).

1. Huber Teaches the Specifically-Recited Signal Sequence Limitations

Retallack anticipates claims 1-2, 18-19 and 21. Retallack discloses the use of *P. fluorescens* signal sequences for directing periplasmic transport of CRM197. (Exh. 1009, [0080]; Exh. 1071, IPR40 ([0078])). Retallack teaches that bacterial host cells can be *Pseudomonas* hosts or *E. coli*. (Exh. 1009, [0047]; Exh. 1071, IPR22 ([0045])). Retallack also teaches that the signal sequences useful for producing CRM197 are not limited to the exemplary *P. fluorescens* signal sequences disclosed in this reference. (Exh. 1009, [0034]; Exh. 1071, IPR19 ([0032])).

Retallack discloses that suitable leader sequences are described in certain patent applications, including U.S. Patent App. Pub. No. 2006/0008877 ("the '877 Publication") (Exh. 1072), which are incorporated by reference. (Exh. 1009, [0033]; Exh. 1071, IPR19 ([0031])). The '877 Publication discloses using *E. coli* signal sequences for periplasmic transport of polypeptides, including in *P. fluorescens* hosts. (Exh. 1072, [0012], [0045], [0079], [0123], [0123]; Exh. 1006, ¶ 141).

Retallack discloses that there is a need for increasing the production yield or expression level of CRM197. (Exh. 1009, [0005]; Exh. 1071, IPR11-12 ([0004])). The disclosure that signal sequences other than the exemplary *P. fluorescens* signal sequences can be used would have motivated POSAs to try additional signal sequences to increase yield. Substitution of one signal sequence for a different one was a routine approach for optimizing protein expression and/or yield. (Exh. 1025, 909, 911). While Retallack shows that significant yields of CRM197 production were achieved, POSAs would have been motivated to use other signal sequences to optimize, and therefore increase these yields. (Exh. 1009, [0085]; Exh. 1071, IPR41-42 ([0083]); Exh. 1006, ¶ 142).

Like Retallack, Huber discloses polynucleotide constructs that encode a polypeptide with signal sequences for use in bacterial host systems. (Exh. 1008, 2984). Huber discloses nine of the thirteen signal sequences recited in the '345 patent claims, including FlgI (which is present in each of claims 4-14, 16-17 and 20), and demonstrates that each of these signal sequences is capable of directing transport of a normally cytoplasmic polypeptide (thioredoxin) to the *E. coli* periplasm. (*Id*., 2983-84, 2987, Fig. 3).[19] Notably, it is these precise nine *E. coli* signal sequences that Huber demonstrates can successfully transport the normally cytoplasmic thioredoxin reporter polypeptide to the periplasm. (*See id*., 2988, Table 2). Huber therefore supplies signal sequences, other than Retallack's exemplary *P. fluorescens* signal sequences, that can be used for periplasmic transport, and provides POSAs with motivation to combine its teachings with Retallack. Also, POSAs would have been motivated to turn to Huber's *E. coli* signal sequences in view of Retallack's teaching that *E. coli* signal sequences can be used in its methods for periplasmic transport of CRM197. (Exh. 1006, ¶ 143).

Huber's positive results were obtained with thioredoxin, a protein that is not normally transported to the periplasm, but is exported to the periplasm in *E. coli* when modified at the N-terminus with a signal sequence. As such, POSAs would have expected that the same signal sequences that can transport thioredoxin would

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[19] Huber states that the signal sequences it utilized were *E. coli* sequences obtained from the publicly accessible SwissProt databank. (*Id*., 2984). PO, too, obtained the amino acid sequences for its signal sequences from a public database (GenEMBL). (Exh. 1001, 19:65-67 & Table 2).

also be able to transport proteins already known to be exportable to the periplasm. Given that DTx mutants, including CRM197, were known to be exportable to the bacterial periplasm, POSAs would have understood that Huber's outcome would apply to DTx mutants, including CRM197. (*Id.*, ¶ 144).

Thus, POSAs would have also had a reasonable expectation that combining the teaching of Retallack and Huber would successfully produce the polynucleotides of claims 4-14, 16-17 and 20. (*Id.*, ¶ 145).

2. The Claim 11 Nucleotide Sequence, Encoding the FlgI Signal Sequence, Would Have Also Been Obvious

Claim 11 recites "wherein the 5' signal sequence portion comprises SEQ ID NO: 23," which is identified as the "[n]ucleotide sequence of the FlgI signal sequence." (Exh. 1001, Fig. 9C). The nineteen amino acid FlgI signal sequence was known (Exh. 1053, 1-2; Exh., 1073; Exh. 1058, 34; Exh. 1006, ¶¶ 146-148) and is 100% identical to the FlgI signal sequence in the '345 patent (Exh. 1001, Fig. 9C, SEQ ID NO 24). The FlgI polynucleotide coding sequence was also known, the first fifty-seven nucleotides of which encode the signal sequence (*i.e.*, the first nineteen FlgI amino acids). (Exh. 1052, 3; Exh. 1073). This polynucleotide encoding this FlgI signal sequence is identical to SEQ ID NO: 23 as recited in claim 11, with the exception of the first base. (Exh. 1006, ¶ 149).

This single base difference, however, does not alter the FlgI signal sequence. Both resulting codons encode methionine. In terms of *E. coli* codon usage, the single base change that yields SEQ ID NO: 23 merely replaces a "suboptimal" codon (GTG) with an "optimal" one (ATG) (AUG in RNA). POSAs would have been motivated to exchange a suboptimal codon for an optimal one using standard codon optimization techniques that were well-known at the time of the '345 patent's earliest effective filing date. (Exh. 1037, 367; Exh. 1046, W126-27). Because the amino acid sequence would not change after codon optimization, POSAs would have reasonably expected to preserve the capability of directing periplasmic transport as described by Huber. (Exh. 1006, ¶ 150).

For the reasons set forth herein, claims 4-14, 16-17 and 20 would have been obvious. *KSR Int'l Co. v. Teleflex Inc*, 550 U.S. 398, 416 (2007).

C. Ground III: Claims 1-2, 18-19 And 21 Of The '345 Patent Are Anticipated By Retallack-719

U.S. Patent No. 9,580,719 to Retallack, et al. ("Retallack-719") issued February 28, 2017 from an application filed on October 30, 2009. (Exh. 1010, IPR1). The '345 patent is not entitled to the October 8, 2009 filing date of GB-647, but only to the next earliest filing date: October 7, 2010. Because Retallack-719's October 30, 2009 filing date predates October 7, 2010, it is prior art under pre-AIA Section 102(e). Retallack-719 was not considered by the Examiner during prosecution of the '345 patent.

Retallack-719 is directed to, *inter alia*, using polynucleotides and bacterial host cells, which can be *P. fluorescens* or *E. coli* cells, for producing a heterologous protein with improved yield and/or quality. (Exh. 1010, abstract, 74:61-75:27). It teaches that the host cells can contain expression vectors or plasmids comprising "a nucleotide sequence encoding a secretion signal sequence polypeptide operably linked to the nucleotide sequence encoding the protein or polypeptide of interest." (*Id*., 46:42-46). The signal sequence is used to achieve periplasmic transport of the polypeptide. (*Id*., 2:63-67; 46:64-47:6). Retallack-719 discloses that periplasmic transport of proteins provides benefits, such as facilitating disulfide bond formation. (*Id*., 47:4-48:10). Retallack-719 identifies certain signal sequences that can be used according to its disclosed methods, and describes plasmids that include such signal sequences. (*Id*., cols. 47-50 (Table 7), 89:54-91:32 (Example 8)). Retallack-719 discloses various "exemplary heterologous proteins that can be expressed" using its disclosed methods, including "[d]iptheria toxin variants, *e.g.* . . . CRM197." (*Id*., 56:44-47, col. 61; Exh. 1006, ¶ 151).

Retallack-719 discloses each and every element of the '345 patent claims 1-2, 18-19, and 21. (Exh. 1006, ¶ 152).

1. Claim 1 Is Anticipated

a. "A polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion"

Retallack-719 teaches the use of a polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion, as required by claim 1 of the '345 patent. Specifically, Retallack-719 discloses that periplasmic expression can be achieved by using "a nucleotide sequence encoding a secretion signal sequence polypeptide [5' signal sequence portion] operably linked to the nucleotide sequence encoding the protein or polypeptide of interest [3' toxin portion]." (Exh. 1010, 46:42-46). Retallack-719 also discloses that the vector comprising the protein coding sequence "further comprises a signal sequence, e.g., a secretion signal sequence." (*Id*., 46:53-56). Retallack-719 also states that in one embodiment, the signal sequence is from *P. fluorescens*. (*Id*., 2:63-65). Such secretion signal sequences can be used to target polypeptides to the bacterial periplasm. (*Id*., 46:64-47:6). Retallack-719 refers to signal sequences as leader sequences, indicating that the signal sequences are at the 5' portion of the polynucleotides and 3' portion of the polynucleotides encodes the polypeptide of interest. (*Id*., 48:11-20). It specifically teaches expression of *Diphtheria* toxin mutants, including CRM197. (*Id*., Table 9, col. 61). Accordingly, Retallack-719 discloses this claim limitation. (Exh. 1006, ¶¶ 153-154).

b. "wherein (a) the 3' toxin portion encodes a mature bacterial toxin polypeptide"

The claim term "encodes a mature bacteria toxin polypeptide" means "contains a polynucleotide that, when translated, yields a bacterial toxin polypeptide lacking a signal peptide." Retallack-719 specifically teaches expression of *Diphtheria* toxin mutants, including CRM197. (Exh. 1010, Table 9, col. 61). Retallack-719 teaches that the signal sequence can be cleaved when the protein is targeted to the periplasm. (*Id*., 46:57-63). Thus, Retallack-719 discloses a 3' toxin portion that encodes a mature bacterial toxin polypeptide, *i.e.*, a toxin polypeptide lacking a signal peptide. (Exh. 1006, ¶¶ 155-156).

c. "having an amino acid sequence at least 90% identical to SEQ ID NO: 32"

Retallack-719's Table 9 specifically lists several exemplary heterologous proteins that can be expressed using its methods—including CRM197. (*Id.*, cols. 61-62). Retallack-719 provides citations listing the well-known amino acid sequence for CRM197 ("Exemplary References/Sequences" which are incorporated by reference). Giannini-1 (cited in Exh. 1010, Table 9 (cols. 61-62)) provides the sequence of CRM197, which is 100% identical to the '345 patent SEQ ID NO: 32. (Exh. 1011, 4066, Fig. 2; Exh. 1006, ¶¶ 157-158). Accordingly, Retallack-719 discloses this claim limitation. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376-77 (Fed. Cir. 2005) (finding anticipation based on disclosure of a claim element in a list in the prior art reference). *See also PubPat Requester v. Abbvie Inc.*, No. 2014-007786, 2015 WL 4038960, at *3 (P.T.A.B. June 30, 2015) (similar).

d. "and (b) the 5' signal sequence portion encodes a polypeptide having an amino acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell"

Retallack-719 teaches that it "may be desirable to target the protein or polypeptide of interest to the periplasm of . . . host cells." (Exh. 1010, 46:40-42). Host cells, according to Retallack-719, can be bacterial cells such as *P. fluorescens* and *E. coli*. (*Id.*, 3:4-7). Retallack-719 further teaches that periplasmic transport can be achieved if "a nucleotide sequence encoding a secretion signal sequence polypeptide" is "operably linked to the nucleotide sequence encoding the protein or polypeptide of interest." (*Id.*, 46:40-46). Retallack-719's Table 7 lists several "Exemplary Leader Sequences," which are described as "useful in the compositions and methods of the present invention." (*Id.*, cols. 47-50, 48:11-13). Retallack-719 also discloses that suitable signal sequences are known in the art. (*Id*., 46:64-67). Thus, Retallack-719 teaches the use of signal sequences to direct transport of polypeptides to the bacterial periplasm. (Exh. 1006, ¶ 159).

Retallack-719 specifically teaches expression of *Diphtheria* toxin mutants, including CRM197. (Exh. 1010, Table 9, col. 61). Accordingly, Retallack-719 teaches an amino acid sequence capable of directing transport of bacterial toxin polypeptides to the bacterial periplasm when expressed in a bacterial host cell. (Exh. 1006, ¶¶ 160-161).

e. "and wherein the 5' signal sequence is not derived from C. *diphtheriae*"

This claim limitation requires that the 5' signal sequence is different in sequence from the signal sequence found in native (not recombinant) *C. diphtheriae*. Retallack-719's Table 7 teaches exemplary "secretion leader sequences useful in the compositions and methods of the present invention." (Exh. 1010, cols. 47-50). Retallack-719 provides the sequences of each of these "secretion leaders." A majority of these signal sequences, such as CupA2, are native to *P. fluorescens*, not *C. diphtheriae.* The CupA2 signal sequence disclosed by Retallack-719 is not found in *C. diphtheriae*. Therefore, Retallack-719 teaches this limitation. (Exh. 1006, ¶ 162).

2. Claim 2 Is Anticipated

Claim 2 recites that "the 3' toxin portion encodes a polypeptide having the amino acid sequence of SEQ ID NO: 32." (Exh. 1001, 49:65-67). SEQ ID NO: 32 of the '345 patent recites the amino acid sequence of CRM197. (*Id.*, Fig. 9E). Retallack-719's Table 9 specifically lists several exemplary heterologous proteins that can be expressed using its methods—including CRM197. (Exh. 1010, col. 61). Retallack-719 provides citations listing the well-known amino acid sequence for CRM197 ("Exemplary References/Sequences" which are incorporated by reference). Giannini-1 (cited in Exh. 1010, Table 9 (cols. 61-62)) provides the sequence of CRM197, which is 100% identical to the '345 patent SEQ ID NO: 32. (Exh. 1011, 4066, Fig. 2; Exh. 1006, ¶¶ 164-165). Accordingly, Retallack-719 discloses this claim limitation.

3. Claim 18 Is Anticipated

Claim 18 recites that "the 3' toxin portion encodes CRM197." (Exh. 1001, 52:34-35). Retallack-719's Table 9 specifically discloses CRM197, and incorporated by reference Giannini-1, which, according to Retallack-719, provides "sequence information" for CRM197. (Exh. 1010, 56:45-48; cols. 61-62). Giannini-1 discloses the sequence of CRM197, and it is 100% identical to the '345 patent SEQ ID NO: 32. (Exh. 1011, 4066, Fig. 2). Accordingly, Retallack-719 discloses this claim limitation. (Exh. 1006, ¶¶ 166-167).

4. Claim 19 Is Anticipated

Claim 19 recites that "the 3' toxin portion encodes a polypeptide having at least 95% sequence identity to SEQ ID NO: 32." (Exh. 1001, 52:36-38). SEQ ID NO. 32 of the '345 patent recites the amino acid sequence of CRM197. (*Id.*, Fig. 9E). Table 9 of Retallack-719 provides "Exemplary References/Sequences" and refers to Giannini-1, which provides the sequence of CRM197 that is 100%, or "at least 95%" identical to the '345 patent SEQ ID NO: 32. (Exh. 1011, 4066, Fig. 2). Accordingly, Retallack-719 discloses this claim limitation. (Exh. 1006, ¶¶ 168-169).

5. Claim 21 Is Anticipated

Claim 21 further recites, "wherein the 5' signal sequence portion is directly 5' of the 3' toxin portion." (Exh. 1001, 52:41-42). Retallack-719 teaches "a nucleotide sequence encoding a secretion signal sequence polypeptide operably linked to the nucleotide sequence encoding the protein or polypeptide of interest." (Exh. 1010, 46:40-46). It also teaches that "[i]n some embodiments, no modifications are made between the signal sequence and the protein or polypeptide of interest." (*Id.*, 46:46-48). POSAs would understand from this disclosure that, where there is no modification, the 5' signal sequence portion is directly 5' of the 3' protein portion. Accordingly, Retallack-719 teaches this claim limitation. (Exh. 1006, ¶¶ 170-171).

D. Ground IV: Claims 1-2, 18-19 And 21 Of The '345 Patent Are Obvious Based On Retallack-719

Retallack-719 teaches each and every limitation of claims 1-2, 18-19 and 21 of the '345 patent. Specifically, Retallack-719 discloses polynucleotides having a 5' signal sequence portion and a 3' toxin portion. It also teaches the claimed signal sequences, which are capable of transporting polypeptides to the periplasm and that these signal sequences are not derived from *C. diphtheriae*. Retallack-719 teaches that one heterologous protein that can be expressed using its disclosed polynucleotides is CRM197. (Exh. 1006, ¶ 172). Therefore, Retallack-719 anticipates claims 1-2, 18-19 and 21. Anticipation is the epitome of obviousness. *Ex parte Numano*, No. 2009-012049, 2010 WL 3198419, at *1 (B.P.A.I. Aug. 11, 2010).

To the extent that it is argued that Retallack-719 does not anticipate the '345 patent claims because Retallack-719 discloses the expression of CRM197 in Table 9 among a list of proteins that can be expressed (*see* Exh. 1010, 56:54-72:38), rather than in an isolated example, Retallack-719 nonetheless renders these claims obvious. Not only does this reference disclose each and every element of these claims, but also POSAs would have been motivated to select CRM197 from Table 9 for direct expression to the periplasm with a reasonable expectation of success. Given the importance of CRM197 to commercial vaccine products, and Retallack-719's teachings regarding the viability of periplasmic expression of polypeptides using its disclosed polynucleotides, POSAs would have been motivated to use the Retallack-719 teachings to make polynucleotides for directing periplasmic transport of CRM197. (*Id.*, 46:40-46). Indeed, Retallack-719 itself teaches that using "secretion signals" leads to several benefits of periplasmic expression, including proper disulfide bond formation and increased yield. (*Id.*, 46:64-48:7). Thus, POSAs would have been motivated to apply Retallack-719's disclosures to obtain the specific CRM197 constructs of the '345 patent. (Exh. 1006, ¶ 173).

POSAs would have had a reasonable expectation of successfully achieving such polynucleotides using the teachings of Retallack-719, because (1) CRM197 is known to be exportable to the periplasm, and (2) Retallack-719 teaches that its signal sequences are capable of transporting polypeptides into the periplasm. In view of these teachings, POSAs would have had a reasonable expectation that Retallack-719's signal sequences are capable of directing periplasmic transport of CRM197. (*Id.*, ¶ 174).

Thus, Retallack-719 discloses the elements of claims 1-2, 18-19 and 21 of the '345 patent and there would have been motivation to use Retallack-719's disclosure to obtain the claimed polynucleotides with a reasonable expectation of success. (*Id.*, ¶ 175).

E. Ground V: Claims 4-14, 16-17 And 20 Would Have Been Obvious Over Retallack-719 And Huber

Claims 4-11, 16-17 and 20 are summarized above. These claims would have been obvious over Retallack-719 in view of Huber. (*Id.*, ¶ 176).

1. Huber Teaches the Specifically-Recited Signal Sequence Limitations

Retallack-719 renders claims 1-2, 18-19 and 21 obvious. While Retallack-719 does not disclose the signal sequences specifically-recited in claims 4-14, 16-17 and 20, Retallack-719 teaches the use of signal sequences to direct periplasmic transport of polypeptides, including CRM197. (Exh. 1010, 46:40-48, Tables 7 & 9). Retallack-719 teaches that bacterial host cells can be *Pseudomonas* hosts, such as *P. fluorescens*, or *E. coli*, which "utilizes expression elements described herein in a manner similar to *P. fluorescens*." (*Id*., 74:60-75:20). Retallack-719 also teaches that the signal sequences "useful in the compositions and methods of the present invention are known in the art and are provided herein and in [the '877 Publication][20] and 2008/0193974, both incorporated herein by reference in [their] entirety." (*Id*., 46:64-47:1; Exh. 1006, ¶ 177).

Retallack-719 discloses the desire to increase the production or yield of

[20] The '877 Publication (Exh. 1072), as discussed above, discloses the use of *E. coli* signal sequences including their use in *P. fluorescens*.

polypeptides. (Exh. 1010, 1:37-47). The disclosure that signal sequences "known in the art" can be used for periplasmic transport of polypeptides, including CRM197, would have motivated POSAs to try additional signal sequences to increase yield. Substitution of one signal sequence for a different one was a routine approach for optimizing protein expression and/or yield. (Exh. 1025, 909, 911; Exh. 1006, ¶ 178).

Both Retallack-719 and Huber disclose polynucleotide constructs that encode a polypeptide with signal sequences for use in bacterial host systems. (Exh. 1008, 2984). Huber demonstrated that nine of the thirteen signal sequences recited in the '345 patent claims, including FlgI (which is present in each of claims 4-14, 16-17 and 20) are capable of directing transport of a normally cytoplasmic polypeptide (thioredoxin) to the *E. coli* periplasm. By supplying signal sequences "known in the art," (which are recited in the claims), Huber provides POSAs with motivation to combine its teachings with Retallack-719. POSAs would have been motivated to turn to Huber's *E. coli* signal sequences in view of Retallack-719's teaching that *E. coli* signal sequences can be used in its methods for periplasmic transport of polypeptides. (Exh. 1010, 46:64-67; Exh. 1072, [0045]; Exh. 1006, ¶ 179).

The knowledge that DTx mutants, including CRM197, were exportable to the bacterial periplasm, coupled with the fact that Huber's positive results were obtained with a protein (thioredoxin) that is normally cytoplasmic, but is capable of being exported when modified at the N-terminus with a signal sequence, would have provided POSAs with a reasonable expectation that combining the teaching of Retallack-719 and Huber would successfully produce the polynucleotides of claims 4-14, 16-17 and 20. (Exh. 1006, ¶ 180).

2. The Claim 11 Nucleotide Sequence, Encoding the FlgI Signal Sequence, Would Have Also Been Obvious

As explained above, the specifically-recited polynucleotide (SEQ ID NO: 23) of claim 11 encodes the FlgI signal sequence. The nineteen amino acid FlgI signal sequence was known (Exh. 1053, 1-2) and is 100% identical to the FlgI signal sequence in the ’345 patent. (Exh. 1001, Fig. 9C, SEQ ID NO 24). The polynucleotide sequence encoding the FlgI signal sequence was also known (Exh. 1052, 3), and is identical to SEQ ID NO: 23 as recited in claim 11, with the exception of the first base. (Exh. 1006, ¶ 181).

The single base difference, however, does not alter the FlgI signal sequence and merely replaces a suboptimal (in terms of expression) codon (GTG) with an optimal one (ATG) (AUG in RNA); such standard codon optimization techniques that were well-known at the time of the ’345 patent’s earliest effective filing date. (Exh. 1037, 367; Exh. 1046, W126-27). POSAs would have been motivated to exchange the suboptimal codon for an optimal one. Because the amino acid sequence would not change after codon optimization, POSAs would have reasonably expected to preserve the capability of directing transport to the periplasm as described by Huber. (Exh. 1006, ¶ 182).

Consequently, for the reasons set forth herein, claims 4-14, 16-17 and 20 would have been obvious. *KSR*, 550 U.S. at 416.

IX. THERE IS NO PROBATIVE EVIDENCE OF SECONDARY CONSIDERATIONS

PO has the burden of establishing secondary considerations of nonobviousness to overcome Petitioner's strong *prima facie* showing of obviousness above. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney Mfg.*, 864 F.2d 757, 768 (Fed. Cir. 1988). And in cases such as this one where a strong prima facie obviousness showing exists, the Federal Circuit has repeatedly held that secondary considerations may not dislodge the primary conclusion of obviousness. *See, e.g., Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Petitioner is not aware of any relevant evidence of secondary considerations. Notably, there is no evidence of the claimed invention achieving unexpected results; POSAs would have expected to achieve periplasmic expression using the claimed polynucleotides. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

To the extent that PO attempts to point to alleged superior results achieved by specific examples, those results lack the necessary nexus to the claims to overcome a *prima facie* case of obviousness. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir.

1995); *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

X. CONCLUSION

Based on the foregoing and the accompanying expert declaration of Dr. DeLisa submitted herewith, claims 1-2, 4-14, and 16-21 of the ’345 patent are anticipated and/or rendered obvious over the prior art cited herein. Petitioner has established a reasonable likelihood of prevailing on each Ground, and favorable resolution of this Petition in favor of Petitioner is respectfully requested.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this proceeding by this firm) to Jones Day Deposit Account No. 50-3013, ref: 122350-610012.

Respectfully Submitted,

Date: November 7, 2018

__/s/ Anthony M. Insogna__
Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel: (858) 314-1200
Fax: (844) 345-3178
Email: MerckGSK-IPRs@jonesday.com

Attorney for Petitioner
Merck Sharp & Dohme Corp

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Petition complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Petition, including footnotes, contains 13,285 words as counted by the word count function of Microsoft Word.

Dated: November 7, 2018

/s/ Anthony M. Insogna

Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel: (858) 314-1200
Fax: (844) 345-3178
Email: MerckGSK-IPRs@jonesday.com

Attorney for Petitioner
Merck Sharp & Dohme Corp.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,422,345, along with all exhibits supporting and filed with the Petition, were served on November 7, 2018, via UPS overnight courier delivery directed to the attorneys of record for the patents at the following addresses:

GlaxoSmithKline
Global Patents UP4110
1250 South Collegeville Road
Collegeville, PA 19426

GlaxoSmithKline
Global Patents
Five Moore Drive
Mail Stop: 5.5A
Research Triangle Park, NC 27709-3398

Date: November 7, 2018

/s/ Anthony M. Insogna

Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel: (858) 314-1200
Fax: (844) 345-3178
Email: MerckGSK-IPRs@jonesday.com

Attorney for Petitioner
Merck Sharp & Dohme Corp