UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC., Petitioner

v.

HOFFMANN-LA ROCHE INC., Patent Owner

United States Patent No. 8,314,225

Case No. IPR2018-01219

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,314,225

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES AND RULES

TABLE OF EXHIBITS

Exhibit No.	***Title***	***Short Cite***
Exhibit 1001	U.S. Patent No. 8,314,225 (filed Nov, 20, 2012).	'225 Patent
Exhibit 1002	Certified File History of U.S. Patent Application No. 12/664,401 (issued as U.S. Patent No. US 8,314,225) (certified on Nov. 3, 2017).	Prosecution History
Exhibit 1003	U.S. Application No. 2002/0160006 (published Oct. 31, 2002).	Denney
Exhibit 1004	World Intellectual Property Organization [WIPO], WO 2007/068429 (June 21, 2007).	Loetscher
Exhibit 1005	U.S. Application No. 2006/0292152 (published Dec. 28, 2006).	Rosenthal
Exhibit 1006	Excerpt from A. Mountain & J.R. Adair, *Engineering antibodies for Therapy*. 10 Biotechnology and Genetic Engineering Reviews 1 (1992).	Mountain & Adair
Exhibit 1007	World Intellectual Property Organization [WIPO], WO 2006/042158 (Apr. 20, 2006).	-
Exhibit 1008	U.S. Patent No. 5,795,965 (filed Dec. 20, 1993).	-
Exhibit 1009	U.S. Application No. 2005/0069552 (published Mar. 31, 2005).	Bleck
Exhibit 1010	M. Gouy & C. Gautier, *Codon usage in bacteria; correlation with gene expressivity,* 10 Nucleic Acids Research 7055 (1982).	Gouy & Gautier
Exhibit 1011	Toshimichi Ikemura, *Codon Usage and tRNA Content in Unicellular and Multicellular Organisms,* 2 Mol. Biol. Evol. 13 (1985).	Ikemura

Exhibit 1012	Yasukazu Nakamura et al., *Codon usage tabulated from international DNA sequence databases: status for the year 2000*, 28 Nucleic Acids Research 292 (2000).	-
Exhibit 1013	World Intellectual Property Organization [WIPO], WO 2009/024567 (Feb. 26, 2009).	-
Exhibit 1014	Joachim Ernst, *Codon usage and gene expression,* 6 Trends in Biotechnology 196 (1988).	-
Exhibit 1015	Claes Gustafsson et al., *Codon Bias and Heterologous Protein Expression,* 22 Trends in Biotechnology 346 (2004).	Gustafsson
Exhibit 1016	Pere Puigbo et al., *"OPTIMIZER: a web server for optimizing the codon usage of DNA sequences,"* 35 Nucleic Acids Research W126 (2007).	Puigbo
Exhibit 1017	World Intellectual Property Organization [WIPO], WO 2007/124077 (Nov. 1, 2007).	-
Exhibit 1018	World Intellectual Property Organization [WIPO], WO 2002/016944 (Feb. 28, 2002).	-
Exhibit 1019	World Intellectual Property Organization [WIPO], WO 2004/083249 (Sept. 30, 2004).	-
Exhibit 1020	World Intellectual Property Organization [WIPO], WO 2001/075110 (Oct. 11, 2001).	-
Exhibit 1021	U.S. Application No. 2004/0063911 (published Apr. 1, 2004).	-
Exhibit 1022	U.S. Patent No. 6,800,735 (filed Apr. 11, 2001).	-
Exhibit 1023	World Intellectual Property Organization [WIPO], WO 2005/077977 (Aug. 25, 2005).	-
Exhibit 1024	U. S. Application No. 2006/0057701 (published Mar. 16, 2006).	-
Exhibit 1025	U.S. Application No. 2006/0204506 (published Sept. 14, 2006).	

Exhibit 1026	World Intellectual Property Organization [WIPO], WO 2006/122822 (Nov. 23, 2006).	-
Exhibit 1027	World Intellectual Property Organization [WIPO], WO 2006/126068 (Nov. 30, 2006).	-
Exhibit 1028	World Intellectual Property Organization [WIPO], WO 2006/126069 (Nov. 30, 2006).	-
Exhibit 1029	U.S. Application No. 2004/0038304 (published Feb. 26, 2004).	-
Exhibit 1030	World Intellectual Property Organization [WIPO], WO 2002/024909 (Mar. 28, 2002).	-
Exhibit 1031	World Intellectual Property Organization [WIPO], WO 2004/060041 (Jul. 22, 2004).	-
Exhibit 1032	Jurgen Haas et al., "*Codon usage limitation in the expression of HIV-1 envelope glycoprotein*," 6 Current Biology 315 (1996).	Haas
Exhibit 1033	Sergei Zolotukhin et al., *A 'Humanized' Green Fluorescent Protein cDNA Adapted for High-Level Expression in Mammalian Cells.* 70 J. Virol. 4646 (1996).	Zolotukhin
Exhibit 1034	Expert Declaration of Dr. Geoffrey Hale, Ph.D., dated June 14, 2018.	Hale
Exhibit 1035	Declaration of Vanessa Park-Thompson in Support of Petitioner's Motion for Admission *Pro Hac Vice*, dated June 14, 2018.	-

I. INTRODUCTION

Pfizer Inc. ("Petitioner" or "Pfizer") requests *inter partes* review of Claims 1-5, 10-12, and 20 (collectively, the "Challenged Claims") of U.S. Patent No. 8,314,225 (the "'225 Patent"; Ex1001), assigned to Hoffmann-La Roche Inc. ("Patent Owner" or "Roche"). The Challenged Claims are unpatentable as anticipated and/or rendered obvious by U.S. Patent Application 2002/0160006 ("Denney"; Ex1003), International Application WO 2007/068429 ("Loetscher"; Ex1004) and U.S. Patent Application 2006/0292152 ("Rosenthal"; Ex1005).

The Challenged Claims purport to claim nucleic acid sequences that encode the C-terminal part of a human immunoglobulin heavy chain and a method for improving the expression of such an immunoglobulin by using the claimed sequences. The independent Challenged Claims, Claims 1 and 20, cover eight specific nucleic acid sequences that purportedly encode the glycine-lysine dipeptide found at the end of human immunoglobulin heavy chains. Contrary to the language of Claims 1 and 20 themselves, two of the claimed sequences inexplicably do **not** encode glycine-lysine, and the claims are therefore invalid on their face. Setting aside these two erroneous sequences, the other six nucleic acid sequences of Claims 1 and 20 are the **only** possible alternatives to replace the naturally-occurring nucleic acid sequence for glycine and still encode the relevant glycine-lysine dipeptide. Accordingly, it is unsurprising that numerous other

investigators had previously disclosed heavy chains with the claimed sequences. The three references detailed herein are just three of many that anticipate and/or render obvious independent Claims 1 and 20.

The '225 Patent's dependent claims narrow the claimed nucleic acid sequences to those that encode the amino acid sequences of naturally-occurring human immunoglobulins, to add a particular nucleic acid before the claimed sequences, to require that the claimed sequences encode a dipeptide near the end of the heavy chain, and to use plasmids and isolated mammalian cells for expressing the immunoglobulins. Such narrowing does not preserve the validity of the dependent claims, as each of these concepts was equally well-known in the prior art.

Each of Denney, Loetscher, and Rosenthal anticipates and/or renders obvious the Challenged Claims under 35 U.S.C. §§ 102 and 103.[1] The Board should grant this Petition and institute trial on all of the Challenged Claims.

II. MANDATORY NOTICES

A. Petitioner and Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

Pfizer is the Real Party-in-Interest. Pfizer is a corporation organized and existing under the laws of Delaware. Its principal place of business is at 235 East 42nd Street, New York, New York 10017.

[1] All references to 35 U.S.C. in this Petition are to the pre-AIA version of the statute.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner identifies the following proceedings of which it is aware that may affect, or be affected by, a decision in this *Inter Partes* Review:

- *Genentech, Inc. and City of Hope v. Sandoz, Inc. et al.*, No. 17-13507 (D. N.J.)
- *Genentech, Inc. and City of Hope v. Pfizer Inc.*, No. 17-1672 (D. Del.)
- Re-examination Control No. 90/014,063

C. Counsel and Service Information (37 C.F.R. § 42.8(b)(3)-(4))

Pfizer's lead and backup counsel are shown below:

- *Lead counsel*: Robert E. Counihan (USPTO Reg. No. 61,382)
- *Backup counsel*: Jeff Oelke (USPTO Reg. No. 37,409)
- *Backup counsel*: Vanessa Park-Thompson*

*Backup counsel to seek *pro hac vice* admission.

Pfizer's service information is shown below:

White & Case LLP	1221 Avenue of the Americas, New York, NY 10020 *Tel.*: (212) 819-8200 *Fax*: (212) 354-8113 *Email*: rcounihan@whitecase.com; joelke@whitecase.com; vanessa.park-thompson@whitecase.com

Please address all correspondence to lead and backup counsel. Pfizer consents to service by email at the email addresses listed above. A power of attorney is being filed concurrently with the designation of counsel in accordance with 37 C.F.R. § 42.10(b).

III. FEES (37 C.F.R. § 42.15(A))

Pfizer authorizes the United States Patent and Trademark Office ("USPTO") to charge $30,500.00 from Deposit Account No. 503672 for the fee set forth in 37 C.F.R. § 42.15(a), and authorizes charging any additional fees associated with this Petition to the same account.

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '225 Patent is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the Challenged Claims on the grounds identified in this Petition.

B. Statement of Relief Requested (37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review, under 35 U.S.C. §§ 311-318 and 37 C.F.R. §§ 42.100-42.123, and cancellation of the Challenged Claims as unpatentable on the following grounds:

Ground	Prior Art	Claims	Basis
1	Denney	1-3, 5, 10-12, 20	§§ 102(b) and 103
2	Loetscher	1-5, 10-12, 20	§§ 102(b) and 103
3	Rosenthal	1-3, 5, 10-12, 20	§§ 102(b) and 103

The full statement of reasons for the relief requested is set forth in detail below. In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith and a Table of Exhibits is provided above. The Expert Declaration of Geoffrey Hale, Ph.D., on behalf of Pfizer, accompanies this Petition. *See* Expert Declaration of Dr. Geoffrey Hale, Ph.D., dated June 14, 2018 ("Hale"; Ex1034). Dr. Hale has extensive experience in the relevant field and is qualified to provide opinions regarding what a person of skill in the art ("POSA") would have known or concluded at the relevant time. *See id.* and Exhibit A thereto.

V. THE LEVEL OF ORDINARY SKILL IN THE ART

The '225 Patent relates to nucleic acid sequences that encode recombinant antibodies and methods using these sequences. A POSA of the '225 Patent as of the priority date would have held a Ph.D. or equivalent (i.e., 4 or 5 years of work

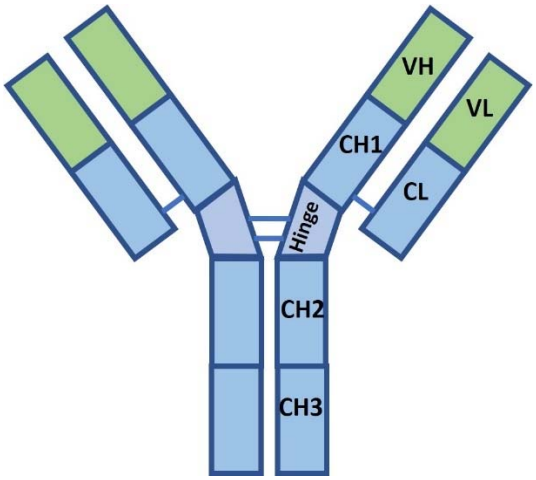
experience) in biochemistry, molecular biology, immunology, or a closely related field. Hale, ¶25. This experience would have included antibody domain and sequence manipulation and swapping, CDR grafting and framework substitution in humanizing antibodies, construction, expression and purification of recombinant antibodies, assays for antibody expression levels and activity and the like. *Id.* The experience may come from the POSA's own experience or through research or work collaborations with other individual(s) with experience in the medicinal, pharmaceutical, or biotech industry, as members of a research team or group. *Id.* For example, the POSA could have worked as part of a team or collaboration to develop antibodies for therapeutic use, including by modifying codons to optimize protein expression systems. *Id.*

VI. THE SCOPE AND CONTENT OF THE PRIOR ART AS OF JUNE 25, 2008

A. Antibody Structure and Sequence

Antibodies are proteins ("immunoglobulins") involved in the immune response. *Id.*, ¶27. There are five different classes of immunoglobulins (IgA, IgD, IgE, IgG and IgM), of which the IgG class is most prevalent. *Id.*, ¶28. The IgG class is further broken down into four subclasses: IgG1, IgG2, IgG3 and IgG4. *Id.*, ¶30.

IgGs are composed of four polypeptide chains: two identical heavy chains and two identical light chains forming the "Y" shaped structure shown below:



Id., ¶28.

Each IgG heavy chain comprises a variable domain (V_H, depicted in green) and three constant domains (C_H1, C_H2 and C_H3, depicted in blue). *Id.*, ¶29. The three constant domains, along with the hinge region, form what is called the "constant region" of the heavy chain. *Id.* Heavy chain constant regions are often referred to according to their corresponding IgG subclass:

IgG Subclass	**Heavy Chain Constant Region**
IgG1	Cγ1
IgG2	Cγ2
IgG3	Cγ3
IgG4	Cγ4

Id., ¶30.

Heavy chains are strings of amino acids. *Id.*, ¶31. The start of the chain is called the "N-terminal end" and the end of the chain is called the "C-terminal end."

Id. Groups of three nucleic acids, called codons, encode each amino acid along the chain. *Id.*

B. Improved Expression of Recombinant Antibodies

Therapeutic antibodies are produced by inserting nucleic acid into a suitable host cell, which then manufactures (or "expresses") the protein. *Id.*, ¶32. Scientists put substantial effort into improving protein expression when engineering antibodies, to ensure economy of manufacture and relative ease of purification. *Id.*; *see also,* A. Mountain & J.R. Adair, *Engineering Antibodies for Therapy*, 10 Biotechnology and Genetic Engineering Reviews 1 (1992) ("Mountain & Adair"; Ex1006) at 24-30.

By June 25, 2008 (the earliest possible priority date for the Challenged Claims), many different factors were known to be relevant when optimizing expression systems. Hale, ¶33. One important consideration was the choice of host cell. *Id.*, ¶33-36; Mountain & Adair at 25. Mammalian cells such as Chinese hamster ovary ("CHO") cells were the most commonly and successfully used host cells, because they provided an efficient and effective means of producing high volumes of recombinant antibodies. *Id*.

Another consideration was the presence of "splicing signals" in genes encoding heavy and light chains. Hale, ¶33, 37-40. The initial gene transcript is like a sentence, telling the cell's protein manufacturing machinery which amino

acids to use to make a given protein. *Id.*, ¶38. Nucleic acid sequences in the gene transcript called "splicing signals" tell the cell where the protein-encoding sequences begin and end. *Id*. In the course of antibody design, scientists may inadvertently introduce sequences similar or identical to splicing signals, leading to unwanted splicing of the initial gene transcript and the formation of aberrant proteins. *Id*. This, in turn, may reduce antibody expression. *Id*.

As of June 2008, POSAs knew that by modifying nucleic acids to destroy an unwanted splice site, they could prevent inadvertent splicing and improve antibody expression. *Id*., ¶39; *see, e.g.,* WO 2006/042158 (Ex1007) (cited in the '225 Patent, 1:66-2:2), Example 4; U.S. Patent No. 5,795,965 (Ex1008), Example 12; US 2005/0069552 ("Bleck"; Ex1009), Example 2. For example, in Bleck, the inventors discovered that the codon "ggt" encoding the penultimate glycine of the heavy chain formed part of the unwanted splice site "g**ggt**" (emphasis on the glycine codon), resulting in the expression of a junk protein. *See* Bleck, Figure 8; Hale, ¶40. To improve protein expression, the inventors altered the nucleic acid sequence to "c**ggg**", where the codon "ggg" still encoded glycine, but the inadvertent splice site was eliminated. *Id*.

One final consideration was the choice of codon to encode a given amino acid. Hale, ¶33, 41. Most of the 20 amino acids are encoded by more than one codon. *Id*., ¶41. Glycine, for example, is encoded by four different codons: ggt,

ggc, gga and ggg. *Id.* As early as the 1980s, researchers had shown that not all codons for the same amino acid are used with the same frequency, and that the most abundantly expressed proteins are encoded by the most commonly-used codons. *Id*., ¶42; *see* M. Gouy & C. Gautier, *Codon usage in bacteria; correlation with gene expressivity*, 10 Nucleic Acids Research 7055 (1982) (Ex1010) at 7070-72. Armed with this knowledge, researchers were able to improve expression by selecting codons that closely approximated the host cell's codon bias. *See, e.g.,* Claes Gustafsson et al., *Codon Bias and heterologous protein expression*, 22 Trends in Biotechnology 346 (2004) (Ex1015) at 346-53; Hale, ¶46. By 2005, free, publicly available computer software could readily and rapidly optimize the codon usage of a given gene to improve its expression level. *See* Pere Puigbo et al., *OPTIMIZER: a web server for optimizing the codon usage of DNA sequences*, 35 Nucleic Acids Research W126 (2007) (Ex1016) at W126-31; Hale, ¶47.

Thus, the choice of host cell, presence of splicing signals and codon bias were all important factors a skilled person would consider when seeking to improve the expression of therapeutic antibodies. *See* Hale, ¶33-48.

VII. THE '225 PATENT

A. The '225 Patent

The '225 Patent, entitled "Heavy Chain Mutant Leading to Improved Immunoglobulin Production," issued on November 20, 2012. It purports to be the

National Stage of International Application No. PCT/EP2008/005136, filed on June 25, 2008. It is assigned to Roche.

The ’225 Patent is concerned with systems for producing recombinant immunoglobulins, and specifically, the possible problem of unwanted splicing leading to aberrant by-products. ’225 Patent, Abstract, 22:26-27, 24:55-56; Hale, ¶49.

In naturally-occurring human immunoglobulin heavy chains, the two amino acids at the C-terminal end are often glycine-lysine and encoded by the codons “ggt” for glycine and “aaa” for lysine (together, “ggtaaa”). Hale, ¶51; *see, e.g.*, ’225 Patent, 6:61-63, Table 1, 8:62-67 and Table 2. Because “ggtaaa” is the nucleic acid sequence in naturally-occurring human IgG heavy chains, it is referred to as the “wild-type” sequence. Hale, *id*. The Patent observes that, when the wild-type sequence, “ggtaaa”, encoded the C-terminal glycine-lysine dipeptide in the single IgG1 antibody disclosed therein, “considerable amounts of an 80 kDa by-product protein were detected.” ’225 Patent, 22:11-14.

Under “Background of the Invention”, the Patent states that codons may be modified to enhance protein expression and/or reduce protein by-products, and cites other patent applications describing success with such techniques. *Id.* at 1:63-2:2. The Patent explains that codon modification “can easily be carried out by a person skilled in the art.” *Id*. at 3:24-25.

The Patent goes on to describe how making a single modification to the glycine at position 4573 of the expression plasmid (changing nucleic acid "t" to "c") using routine codon modification techniques eliminated the 80 kDa by-product. '225 Patent, 19:31-32, 22:26-29; Hale, ¶53. Aside from this one change, the inventors left the naturally-occurring human heavy chain intact. *Id*.

The Patent does not explain or analyze the source of the 80 kDa by-product or its elimination, except to note, in passing, that the single codon modification may have destroyed an inadvertent splice site. '225 Patent, 22:26-27, 24:55-60; Hale, *id*. This is the same problem and same solution addressed by previous researchers like Bleck and others, as explained above in § VI.B. Hale, *id*.

B. The Challenged Claims

i. *Challenged Claim 1*

Independent Claim 1 is directed at a nucleic acid encoding a glycine-lysine dipeptide in an antibody heavy chain. It reads (broken down into its constituent elements):

> *A nucleic acid encoding the amino acid sequence of the C-terminal part of the C_H3-domain of an immunoglobulin of the class IgA or IgG, or the amino acid sequence of the C-terminal part of the C_H4-domain of an immunoglobulin of the class IgE or IgM,*
>
> *wherein the glycine-lysine-dipeptide comprised in said amino acid sequence of the C-terminal part of the C_H3- or C_H4-domain is encoded by one of the following nucleic acid sequences, ggaaca, ggcaac, gggaaa, ggaaag, ggcaag, and gggaag, the nucleic acid ggaaaa, or the nucleic acid ggcaaa.*

'225 Patent, 39:47-56.

Claim 1 claims eight specific nucleic acid sequences. Contrary to the language of Claim 1 itself, two of the claimed sequences do not encode glycine-lysine. Hale, ¶55. Specifically, "ggaaca" encodes glycine-threonine and "ggcaac" encodes glycine-arginine; thus, neither sequence encodes glycine-lysine as Claim 1 requires. *Id*. Neither the patent specification nor the prosecution history explains this error. *Id*. Therefore, the claim language "wherein the glycine-lysine-dipeptide . . . is encoded by one of the following nucleic acid sequences, ggaaca, ggcaac . . ." is invalid on its face.

With the exception of these two erroneous codon pairs, the remaining six codon pairs are the only other possible sequences to replace the wild-type glycine sequence "ggt" and still encode the C-terminal glycine-lysine dipeptide normally found in human immunoglobulin heavy chains. *Id.*, ¶57. Unsurprisingly, these alternative sequences had previously been made and disclosed by numerous other investigators in the course of codon optimization or otherwise, as reviewed in § X.A, below. *Id*.

The Patent itself does not disclose making or using any of the following claimed nucleic acid sequences to encode the glycine-lysine dipeptide: "gggaaa", "ggaaag", "ggcaag", "gggaag" or "ggaaaa". *Id.*, ¶56. The Examples only use "ggcaaa". *Id.*; *see* '225 Patent, 22:60-61, 24:28-29.

ii. ***Challenged Dependent Claims***

Challenged Claims 2-5 and 10-12 depend directly or indirectly from Claim 1.

Claim 2 claims seven specific amino acid sequences encoded by the nucleic acid of Claim 1. As shown in the table below, the claimed amino acid sequences are simply the sequences of the C-terminal part of the C_H3-domain (for IgA, IgG1, IgG2, IgG3 and IgG4) or C_H4-domain (for IgM or IgE) in naturally-occurring human immunoglobulins and were well-known in the prior art.

SEQ ID in '225 Patent, Claim 2	**Wild-Type Human Immunoglobulin**
1	IgA
3	IgE
4	IgM
5	IgG1
6	IgG2
7	IgG3
8	IgG4

See, e.g., WO 2007/124077 (Ex1017), Figures 2 and 3; Hale, ¶60.

Claim 3 depends from Claim 2 and requires that the nucleotide "g" or "a" precede the glycine-lysine dipeptide. Hale, ¶62. Nothing in the '225 Patent or in the prosecution history explains the reason for this additional limitation or whether

it adds any benefit. *Id*. In human immunoglobulins, the amino acid that precedes the C-terminal glycine-lysine dipeptide may be alanine (encoded by "gc**g**"), proline (encoded by "cc**c**" or "cc**g**"), threonine (encoded by "ac**c**"), or leucine (encoded by "ct**g**"). *See, e.g.,* '225 Patent, 6:61-63, Table 1, 8:62-67, Table 2; Hale, *id*. Given the dependency of Claim 3 on Claim 2, and the requirement in Claim 2 that the nucleic acid encode an immunoglobulin, Claim 3 seemingly only narrows Claim 2 by requiring that the preceding amino acid be alanine, proline or leucine (and not threonine). Hale, *id*.

Claim 4 further depends from Claim 3 and requires that the glycine-lysine dipeptide be encoded by "ggaaaa", "ggcaaa" or "gggaaa". The sequences of Claim 4 are simply a subset of those in Claim 1, limited to the three non-wild-type glycine sequences ("gga", "ggc" and "ggg") combined with the wild-type lysine sequence ("aaa"). *Id*., ¶64. Neither the Patent nor the prosecution history explains why this particular subset has been chosen or whether it adds any benefit. *Id*.

Claim 5 limits the C-terminal part of the heavy chain of Claim 1 to "at least the 20 C-terminal amino acids of the immunoglobulin heavy chain primary amino acid sequence." As set forth below, in each of Petitioner's prior art references, glycine and lysine are always the last two amino acids of the heavy chain; thus, the glycine-lysine dipeptide is necessarily located within the last 20 C-terminal amino acids. *Id*., ¶66.

Claims 10 to 12 claim standard techniques for expressing the nucleic acids of Claim 1, namely, using plasmid expression vectors and isolated mammalian cells that were widely used for this purpose by the early 1990s. *Id.*, ¶68. The Patent admits that the expression systems it discloses and claims were "well-known and reported in the state of the art literature." *See, e.g.*, '225 Patent, 1:16-23, 3:11-17, 12:64-13:10.

iii. ***Challenged Claim 20***

Independent Claim 20 claims a method for inserting the same nucleic acids as Claim 1 into a mammalian cell (called "transfection") and then expressing and recovering the immunoglobulin. Hale, ¶69. It reads (broken down into its constituent elements):

> *A method for improving the expression of an immunoglobulin in a mammalian cell, comprising the following steps:*
>
> *a) transfecting a mammalian cell with a nucleic acid encoding an immunoglobulin heavy chain,*
>
> *wherein the nucleic acid encoding the immunoglobulin heavy chain comprises the nucleic acid ggaaaa, or the nucleic acid ggcaaa, or the nucleic acid gggaaa, or the nucleic acid ggaaag, or the nucleic acid ggcaag, or the nucleic acid gggaag encoding the glycine-lysine-dipeptide contained in the C_H3- or C_H4-domain of the immunoglobulin heavy chain,*
>
> *b) cultivating the transfected mammalian cell under conditions suitable for the expression of the immunoglobulin,*
>
> *c) recovering the immunoglobulin from the culture or the cell.*

As the Patent admits, the claimed method was the standard procedure for recombinantly synthesizing an antibody as of June 2008, using the only possible sequences available to replace the wild-type glycine sequence "ggt" and still encode the C-terminal glycine-lysine dipeptide normally found in human immunoglobulin heavy chains. *See, e.g.,* '225 Patent, 12:64-66, 12:31-35; Hale, ¶70-71; *see also* Denney, ¶276-305, 323, 355-360; Loetscher, p. 64-72; Rosenthal, ¶215.

C. The Prosecution History

The '225 Patent issued on November 20, 2012 from U.S. Application No. 12/664,401.

To Petitioner's knowledge, none of the prior art cited in this Petition (Denney, Rosenthal and Loetscher) was considered during prosecution. The sole Office Action issued during prosecution rejected certain claims under 35 U.S.C. § 101 (non-statutory subject matter) and § 112 (indefiniteness), and for informalities in the claims (i.e., redundancies and inconsistencies). *See* Prosecution History (Ex1002), at 1252-57 (04/05/12 Office Action). The Examiner did not make any rejections based on prior art.

In response to the above referenced Office Action, the Applicant amended the claims to overcome the issues the USPTO had noted. *See id*. at 1304-10 (07/05/12 Amendment and Response). In particular, the Applicant deleted the

redundant sequences, corrected an erroneous claim dependency, and modified the language of certain claims to avoid the §§ 101 and 112 rejections. *Id.* at 1309-10.

The USPTO issued the Notice of Allowance without further comment. *See id*. at 1314-16 (07/19/12 Notice of Allowance).

VIII. CLAIM CONSTRUCTION

In an IPR, the Board construes claim terms according to the broadest reasonable interpretation ("BRI"), consistent with their plain meaning in the context of the written description and the prosecution history. 37 C.F.R. § 42.100(b) (2012); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016); *Medrad, Inc. v. MRI Devices Corp*., 401 F.3d 1313, 1318 (Fed. Cir. 2005).[2]

For the purposes of this proceeding, Petitioner does not request construction of any claim, but addresses the preamble of Claim 20 to the extent that Patent Owner seeks such a construction. Petitioner does not waive any right to seek additional or alternative constructions in any other forum.

Claim 20 contains the following preamble: "A method for improving the expression of an immunoglobulin in a mammalian cell, comprising the following steps . . ." A preamble is generally not limiting when the rest of the claim describes a structurally complete invention and the preamble only states a purpose or

[2] The PTO has proposed to replace the BRI standard with the standard used by Article III federal courts following *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). As described herein, Petitioner submits that the proper construction of Claim 20 is the same under either the BRI or *Phillips* standards.

intended use for the invention. *Catalina Mktg. Int'l v. Coolsavings.com*, *Inc*., 289 F.3d 801, 808-809 (Fed. Cir. 2002); *STX, LLC v. Brine, Inc*., 211 F.3d 588, 591 (Fed. Cir. 2000). "[P]reamble language merely extolling benefits or features of the claimed invention does not limit the claim scope without clear reliance on those benefits or features as patentably significant." *Catalina Mktg., id.*

The preamble to Claim 20 is not a claim limitation, as "improving" immunoglobulin expression merely states the desired effect of the claimed method and not the invention itself. Hale, ¶74. Nothing in the Patent or the prosecution history shows "clear reliance" on the preamble as a patentably significant aspect of the claims. *Id*. Thus, the preamble is not a claim limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co*., 182 F.3d 1298, 1305 (Fed. Cir. 1999).

The Board's BRI standard further supports this conclusion as, in the broadest view, a preamble should be considered non-limiting. *See In re Taylor*, 484 F. App'x 540, 543-44 (Fed. Cir. 2012) (upholding the Board's determination that the preamble was non-limiting, in light of the BRI standard); *see also In re Montgomery*, 677 F.3d 1375, 1380-81 (Fed. Cir. 2012) (concluding, in dicta, that construing a preamble as non-limiting "is even more appropriate here in the examination context, where we apply the 'broadest reasonable interpretation consistent with the specification'").

If the Board determines that the preamble **is** a claim limitation, then, giving Claim 20 its broadest reasonable interpretation (or equally, its plain and ordinary meaning), the claimed "method for improving the expression of an immunoglobulin in a mammalian cell" would, at minimum, include codon modification. Hale, ¶75. Codon modification is the only method described in the '225 Patent to "improv[e] the expression of an immunoglobulin in a mammalian cell". Specifically, the Patent describes modifying a particular dipeptide away from the wild-type sequence to eliminate a by-product and thus improve expression. *Id.*; *see, supra*, § VII.A; '225 Patent, 13:37-45, 22:26-29. The Patent also highlights publicly available references where codons were modified to enhance protein expression and reduce protein by-products. '225 Patent, 1:63-2:2. Thus, a POSA would understand the broadest reasonable interpretation (or the plain and ordinary meaning) of Claim 20's preamble to include codon modification. Hale, ¶76.

Pfizer's proposed construction should be adopted as it is consistent with the '225 Patent and the POSA's understanding.

IX. LEGAL STANDARDS

For the purposes of this proceeding, Petitioner does not challenge the '225 Patent's effective filing date, June 25, 2008 (the filing date of PCT/EP2008/005136, of which the '225 Patent is the national stage application).

35 U.S.C. § 363. Although the '225 Patent also claims priority to EP07012774, that foreign application is only available to predate references dated after June 29, 2007. All references in the Grounds in this Petition are dated prior to June 21, 2007.

A patent is invalid for anticipation where a "single prior art reference discloses, either expressly or inherently, each limitation of the claim." *Brassica Protection Prods. LLC v. Sunrise Farms* (*In re Cruciferous Sprout Litig.*), 301 F.3d 1343, 1349 (Fed. Cir. 2002). "When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F3d 1349, 1351 (Fed. Cir. 2001). "[I]n considering the disclosure of a reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A patent claim is invalid under § 103(a) if the subject matter as a whole would have been obvious to a POSA at the time the claimed invention was made. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Although anticipation and obviousness are distinct doctrines, anticipation is the "epitome of obviousness," and a patent challenger can use the same reference to argue that a claim is both

anticipated and obvious. *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1363 (Fed. Cir. 2008); *see also In re Meyer*, 599 F.2d 1026, 1031 (C.C.P.A. 1979). Indeed, "it is commonly understood that prior art references that anticipate a claim will usually render that claim obvious." *Cohesive Techs., id.*, at 1364. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. § 103 and for anticipation under 35 U.S.C. § 102." *In re Best*, 562 F.2d 1252, 1255 n.4 (C.C.P.A. 1974).

X. DETAILED STATEMENT OF GROUNDS FOR INVALIDITY

This Petition must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2012). As described below, this Petition meets and exceeds this threshold.

Pursuant to *SAS Institute Inc. v. Iancu*, 200 L.Ed.2d 695 (U.S. 2018), this Petition should be instituted as to all of the Challenged Claims.

A. Numerous Prior Art References Teach the Sequences, Systems and Methods of the Challenged Claims

Numerous prior art references in the early 2000s describe antibodies or other proteins where the C-terminal glycine-lysine dipeptide was encoded by the nucleic acid sequences claimed in Claims 1 and 20 of the '225 Patent. Hale, ¶78. These same references also disclose the amino acid sequences claimed in dependent

Claim 2 of the Patent. *Id.* The below chart provides just a few examples of this considerable body of prior art that anticipates the Challenged Claims:

Prior Art Reference	**Relevant Nucleic Acid SEQ ID in Prior Art Reference**	**Relevant Amino Acid SEQ ID in Prior Art Reference**	**Gly-Lys Codon Pair of '225 Patent, Claims 1, 20 Disclosed in Prior Art Nucleic Acid SEQ ID**	**Amino Acid SEQ ID of '225 Patent, Claim 2 Disclosed in Prior Art Amino Acid SEQ ID**
Denney U.S. Application No. 2002/0160006 (published Oct. 31, 2002)	44	45	ggcaag	7
	46	47	ggcaag	8
Loetscher WO 2007/068429 (published Jun. 21, 2007)	23	6	ggcaaa	5
Rosenthal U.S. Application No. 2006/0292152 (published Dec. 28, 2006)	13	11	ggaaag	6
Bleck U.S. Application No. 2005/0069552 (published Mar. 31, 2005)	15	15 - inherent	gggaaa	8
WO 2004/083249 (published Sept. 30,	38	37	ggaaaa	5

Prior Art Reference	Relevant Nucleic Acid SEQ ID in Prior Art Reference	Relevant Amino Acid SEQ ID in Prior Art Reference	Gly-Lys Codon Pair of '225 Patent, Claims 1, 20 Disclosed in Prior Art Nucleic Acid SEQ ID	Amino Acid SEQ ID of '225 Patent, Claim 2 Disclosed in Prior Art Amino Acid SEQ ID
2004) (Ex2019)				
WO 2001/075110 (published Oct. 11, 2001) (Ex1020)	27	26	ggaaaa	5
US 2004/0063911 (published Apr. 1, 2004) (Ex1021)	49	50	gggaaa	5
U.S. 6,800,735 (published Oct. 4, 2004) (Ex1022)	41	42	gggaaa	5
	43	44	gggaaa	5
WO 2005/077977 (published Aug. 25, 2005) (Ex1023)	25	46	ggcaag	5
US 2006/0057701 (published Mar. 16, 2006) (Ex1024)	38	36	ggaaag	6
US 2006/0204506 (published Sept. 14, 2006) (Ex1025)	1	2	gggaaa	5
	5	6	gggaaa	5
	9	10	gggaaa	5
WO 2006/122822 (published Nov. 23, 2006) (Ex1026)	1	2	ggcaag	8

Prior Art Reference	Relevant Nucleic Acid SEQ ID in Prior Art Reference	Relevant Amino Acid SEQ ID in Prior Art Reference	Gly-Lys Codon Pair of '225 Patent, Claims 1, 20 Disclosed in Prior Art Nucleic Acid SEQ ID	Amino Acid SEQ ID of '225 Patent, Claim 2 Disclosed in Prior Art Amino Acid SEQ ID
WO2006/126068 (published Nov. 30, 2006) (Ex1027)	6	6	ggaaag	5
WO 2006/126069 (published Nov. 30, 2006) (Ex1028)	3	3	ggcaag	5
US 2004/0038304 (published Feb. 26, 2004) (Ex1029)	1	Fig. 5	gggaaa	5
	2	Fig. 5	gggaaa	5
WO 2002/024909 (published Mar. 28, 2002) (Ex1030)	11	12	gggaaa	5
WO 2004/060041 (published Jul. 22, 2004) (Ex1031)	Example 4	Example 4	gggaaa	5

Id.

In each of the above references, the sequence encoding the glycine-lysine dipeptide at the end of the heavy chain is different from the wild-type sequence ("ggtaaa"). While the reason for this change is not always explicitly stated, several authors explain that they employed common codon modification techniques as part

of routine codon optimization efforts. *See, e.g.*, Denney, ¶329; WO 2005/077977 (Ex1023), 14:19-24; WO 2006/122822 (Ex1026), 1:4-8, 26:12-17; WO2006/126068 (Ex1027), p. 1, 5; WO 2006/126069 (Ex1028), p. 5; *see also* Hale, ¶79.

The extent of anticipatory prior art is therefore not surprising, as it was well known by June 2008 that codon optimization could improve protein expression because the most abundantly expressed proteins are encoded by the most frequently used codons. Gouy & Gautier at 7070-72; *see also* Hale, ¶42, 80. Researchers often modified the recombinant nucleic acid sequence to align it with the most frequently used codons of the expression system, while maintaining the amino acid sequence. Hale, ¶46-48, 79; Gustaffson at 348.

Relevant here, long before June 2008, Ikemura's public database had shown that the codon bias in human and CHO sequences was GGC>GGG=GGA>GGT for glycine and AAG>AAA for lysine. Toshimichi Ikemura, *Codon Usage and tRNA Content in Unicellular and Multicellular Organisms*, 2 Mol. Biol. Evol. 13 (1985) (Ex1011) at 13-32; Hale, ¶43-45, 80. In other words, Ikemura taught that the wild-type nucleic acid sequence "ggtaaa" actually comprises the **least** preferred codons for both glycine and lysine in mammalian cells. *Id*. A POSA would recognize that modification to more preferred codons could increase immunoglobulin expression, and therefore that any of the three alternatives to the

wild-type glycine codon or the one alternative to the wild-type lysine codon (or some combination of the two) could improve protein expression. Hale, ¶80.

For simplicity, this Petition does not analyze each of the prior art references identified above. Instead, it focuses on three particular prior art references (Denney, Loetscher and Rosenthal) that anticipate and/or render obvious each of the Challenged Claims as follows:

Prior Art	Publication Date	Gly-Lys Codon Pair	Base Before Gly-Lys	Nucleic Acid SEQ ID	Amino Acid SEQ ID	Identical SEQ ID in '225 Patent
Denney	10/31/2002	ggcaag	c	44	45	7
Denney	10/31/2002	ggcaag	g	46	47	8
Loetscher	06/21/2007	ggcaaa	g	23	6	5
Rosenthal	12/28/2006	ggaaag	a	13	11	6

B. Ground 1: Denney Anticipates and/or Renders Obvious the Challenged Claims

Denney provides nucleic acid and amino acid sequences for IgGs derived from B-cell lymphoma cells and methods for expressing them. *See* Denney, Abstract, ¶329, 355-360; Hale, ¶81. The inventors' stated goal was to produce and purify tumor-specific IgG3s or IgG4s. *See* Denney, ¶360; Hale, ¶82. Denney used codon optimization to obtain high levels of immunoglobulin expression, modifying the constant regions to use codons found most frequently in highly expressed mammalian proteins. *See* Denney, ¶329, Hale, ¶83.

To Petitioner's knowledge, Denney was not cited during prosecution.

Denney was published on October 31, 2002 and was publicly available more than one year before the effective filing date for determining whether a reference qualifies as § 102(b) prior art (June 25, 2008, hereafter the "effective filing date"). It is therefore § 102(b) prior art.

i. ***Denney Anticipates Claim 1***

Denney expressly discloses every requirement of Claim 1. Denney discloses the first limitation of Claim 1:

> *"A nucleic acid encoding the amino acid sequence of the C-terminal part of the C_H3-domain of an immunoglobulin of the class IgA or IgG, or the amino acid sequence of the C-terminal part of the C_H4-domain of an immunoglobulin of the class IgE or IgM…"*

Hale, ¶94.

SEQ ID NO:44 of Denney discloses a nucleic acid encoding an IgG3's Cγ3 region. Denney, ¶322, 329; Hale, ¶95. The Cγ3 region is the entire constant region (the C_H1-domain, hinge, C_H2-domain and C_H3-domain) of the IgG3, including the C-terminal part of the C_H3-domain.[3] *Id*.; *see also* § VI.A, *supra*.

[3] In Petitioner's view, the term "the C-terminal part of the C_H3- or C_H4-domain" does not require construction for the purposes of this Petition. However, if the Board finds any ambiguity in its meaning, Petitioner notes that in each of the three prior art references discussed in this Petition, the claimed nucleic acid encodes the **final two amino acids** in the C_H3-domain (*see* Denney, SEQ ID NOs:45 and 47; Loetscher, SEQ ID NO:6; Rosenthal, SEQ ID NO:11). Therefore, regardless of how the Board construes this term, it must be met by each of Denney, Loetscher,

Similarly, SEQ ID NO:46 of Denney discloses a nucleic acid encoding an IgG4's Cγ4 region. Denney, ¶322, 329; Hale, ¶96. The Cγ4 region is the entire constant region of the IgG4, including the C-terminal part of the C_H3-domain. *Id.*; *see also* § VI.A, *supra*.

Denney also discloses the sequence "**ggcaag**" of the second limitation of Claim 1 (emphasis added):

> *"wherein the glycine-lysine-dipeptide comprised in said amino acid sequence of the C-terminal part of the C_H3- or C_H4-domain is encoded by one of the following nucleic acid sequences, ggaaca, ggcaac, gggaaa, ggaaag, **ggcaag**, and gggaag, the nucleic acid ggaaaa, or the nucleic acid ggcaaa."*

Hale, ¶97.

In Denney, amino acid SEQ ID NO:45 corresponds to nucleic acid SEQ ID NO:44. Denney, ¶329; Hale, ¶98. The C-terminal amino acids of Denney's SEQ ID NO:45, with the glycine-lysine dipeptide at the end, are shown below (highlight added):

```
<210> SEQ ID NO 45
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    370                 375
```

---

and Rosenthal. Petitioner reserves all rights to challenge, in any forum, any interpretation of any claim term Patent Owner may offer.

The C-terminal glycine-lysine dipeptide of Denney's amino acid SEQ ID NO:45 is encoded by "ggcaag", which is one of the codon pairs in Claim 1. *See* Denney, SEQ ID NO:44, nucleotides 1131 to 1136; Hale, ¶99. The relevant portion of Denney's nucleic acid SEQ ID NO:44 is shown below (highlight added):

<210> SEQ ID NO 44
<211> LENGTH: 1147
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 44

aagctgaccg tggacaagag ccgctggcag cagggcaaca tcttctcctg cagcgtgatg 1080

catgaggccc tgcacaaccg cttcacccag aagagcctga gcctgagccc cggcaagtga 1140

tagatct 1147

Similarly, Denney's amino acid SEQ ID NO:47 corresponds to nucleic acid SEQ ID NO:46. Denney, ¶329; Hale, ¶100. The C-terminal amino acids of Denney's SEQ ID NO:47, with the glycine-lysine dipeptide at the end, is shown below (highlight added):

<210> SEQ ID NO 47
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Leu Ser Leu Ser Leu Gly Lys
325

The C-terminal glycine-lysine dipeptide comprised in Denney's amino acid SEQ ID NO:47 is encoded by "ggcaag", which is one of the codon pairs in Claim 1. *See* Denney, SEQ ID NO:46, nucleotides 974 to 979; Hale, ¶101. The relevant portion of Denney's nucleic acid SEQ ID NO:46 is shown below (highlight added):

<210> SEQ ID NO 46
<211> LENGTH: 999
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

aggagggcaa cgtgttctcc tgctccgtga tgcatgaggc cctgcacaac cactacaccc 960

agaagagcct gagcctgagc ctggcaagt gatagatct 999

Thus, Denney discloses all limitations of and anticipates Claim 1. Hale, ¶102.

ii. ***Denney Anticipates Claim 2***

Claim 2 depends from Claim 1 and contains the following additional limitation:

> *"The nucleic acid of claim 1, wherein said nucleic acid encodes an amino acid sequence selected from the amino acid sequences of SEQ ID NO: 1, 3, 4, 5, 6, 7, or 8."*

Denney anticipates Claim 2 by expressly disclosing the nucleic acids of Claim 1 that encode amino acid SEQ ID NOs:7 and 8 of the '225 Patent. Hale, ¶103.

As explained above, the nucleic acid claimed in Claim 1 is disclosed in Denney's SEQ ID NO:44 and the corresponding amino acid sequence is Denney's SEQ ID NO:45. Denney, ¶329; Hale, ¶104. As shown below, Denney's SEQ ID NO:45 is identical to **SEQ ID NO:7** of the '225 Patent, anticipating Claim 2:

```
  >  DENNEY  SEQ ID NO:45
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTT
PPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK

  > '225 Patent SEQ ID No:7 (Table 1)
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTT
PPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
```

Hale, ¶105.

Similarly, as explained above, the nucleic acid claimed in Claim 1 is disclosed in Denney's SEQ ID NO:46 and the corresponding amino acid sequence is Denney's SEQ ID NO:47. Denney, ¶329; Hale, ¶106. Denney's SEQ ID NO:47 is identical to **SEQ ID NO:8** of the '225 Patent, anticipating Claim 2:

```
    >  DENNEY  SEQ ID NO:47
GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

    > '225 Patent SEQ ID No:8
GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
```

Hale, ¶107.

iii. *Denney Anticipates Claim 3*

Claim 3 further depends from Claim 2 and contains the following additional limitation:

"The nucleic acid of claim 2, wherein the nucleic acid encoding said glycine-lysine-dipeptide is preceded by the nucleotide g or a."

As explained above, Denney's SEQ ID NO:46 discloses the nucleic acid claimed in Claim 2. *See, supra*, §X.B.iii; Hale, ¶110. In Denney's SEQ ID NO:46, the nucleic acid encoding the glycine-lysine dipeptide, "ggcaag", is preceded by the nucleotide "g". The relevant portion of Denney's SEQ ID NO:46 is shown below ("g" highlighted in green):

<210> SEQ ID NO 46
<211> LENGTH: 999
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

aggagggcaa cgtgttctcc tgctccgtga tgcatgaggc cctgcacaac cactacaccc 960

agaagagcct gagcctgagc ctgggcaagt gatagatct 999

Id.

Thus, Denney anticipates Claim 3. Hale, ¶111.

iv. ***Denney Anticipates Claim 5***

Claim 5 depends from Claim 1 and contains the following additional limitation:

"The nucleic acid of claim 1, wherein the C-terminal part of the C_H3 domain, or the C-terminal part of the C_H4 domain, comprises at least the 20 C-terminal amino acids of the immunoglobulin heavy chain primary amino acid sequence."

Denney expressly discloses nucleic acids of Claim 1 that meet this limitation. Hale, ¶112. As explained above regarding Claim 1, Denney's SEQ ID NOs:44 and 46 both disclose the nucleic acid of Claim 1. Hale, ¶94-102. Denney's nucleic acid SEQ ID NOs:44 and 46 each encode the entire C_H3-domain of Cγ3 or Cγ4, respectively. *See* Denney, ¶329; Hale, ¶113. Denney's SEQ ID NOs:44 and 46 therefore include at least the 20 C-terminal amino acids of the respective heavy chain amino acid sequences (i.e., the final 20 amino acids at the C-terminus of the amino acid sequence) to which they correspond, i.e. Denney's SEQ ID NOs:45 and 47. *Id.* The images below show the entirety of Denney's SEQ ID Nos:45 and 47:

> DENNEY SEQ ID NO:45
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTT
PPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK

> DENNEY SEQ ID NO:47
GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

The glycine-lysine dipeptide falling at the very end of the amino acid sequences comes within the **last 20 amino acids**. *Id*. Thus, Denney anticipates Claim 5. *Id*.

v. ***Denney Anticipates Claim 10***

Claim 10 claims:

"A plasmid comprising the nucleic acid of claim 1."

Denney expressly discloses plasmids that meet this claim. Hale, ¶114. Denney states that the **plasmid pSRαSD9cG3C** contains nucleic acid SEQ ID NO:44 and the **plasmid pSRαSD9CG4C** contains nucleic acid SEQ ID NO:46. Denney, ¶329; Hale, ¶115. As described above, nucleic acid SEQ ID NOs:44 and 46 meet the requirements of Claim 1. Hale, ¶94-102. Thus, Denney anticipates Claim 10. Hale, ¶115.

vi. *Denney Anticipates Claim 11*

Claim 11 claims:

> *"An isolated cell comprising the nucleic acid of claim 1, wherein said cell is a mammalian cell."*

Denney expressly discloses isolated mammalian cells that meet this claim. Hale, ¶116. First, Denney describes the isolation and cloning of IgG heavy chain variable regions using the plasmids pSRαSD9cG3C or pSRαSD9CG4C. *See* Denney, ¶351; Hale, ¶117. As described above regarding Claim 10, pSRαSD9cG3C and pSRαSD9CG4C comprise the nucleic acid of Claim 1. Denney, ¶329; Hale, *id*.

These plasmids are then used to transfect ("electroporate") the **mammalian** (mouse) BW5147.G.1.4 **cell line**. *See* Denney, ¶358; Hale, ¶118. Denney explains that other mammalian cell lines may also be used for this purpose, including CHO cells. *See* Denney, ¶26, 159; Hale, ¶120.

Finally, the transfected cells are **isolated** by cloning and selected for their ability to express the IgG encoded by the nucleic acid of Claim 1. *See* Denney, ¶358; Hale, ¶119.

Thus, Denney anticipates Claim 11. Hale, ¶120.

vii. *Denney Anticipates Claim 12*

Claim 12 further depends from Claim 11 and contains the following additional limitation:

> *"The cell of claim 11, characterized in that said mammalian cell is selected from a CHO cell, a HEK cell, or a BHK cell."*

Denney expressly discloses isolated CHO cells that meet this claim. Hale, ¶121. Denney explains that "[a] variety of mammalian cell lines may be employed for the expression of recombinant proteins according to the methods of the resent [sic] invention. Exemplary cell lines include **CHO cell lines** . . ." *See* Denney, ¶159 (emphasis added); Hale, ¶122.

As described above, Denney discloses the nucleic acid of Claim 1 and the cell of Claim 11. Hale, *id*. Thus, Denney anticipates Claim 12. *Id*.

viii. *Denney Anticipates Claim 20*

Denney expressly discloses every requirement of Claim 20 and therefore anticipates it. Hale, ¶123.

Claim 20 begins with the preamble:

> *"A method for improving the expression of an immunoglobulin in a mammalian cell, comprising the following steps…"*

The preamble merely sets out the purpose of the alleged invention and is not a claim limitation. *See* § VIII, *supra*; Hale, ¶124. Steps (a), (b) and (c) of Claim 20 are simply the plasmid and host cells of Claims 10-12 for expression of the nucleic acid claimed in Claim 1, all of which Denney discloses. *See* § X.B.i, v-vii, *supra*; Hale, ¶127. Denney therefore anticipates Claim 20. *Marrin v. Griffin*, 599 F.3d 1290, 1295 (Fed. Cir. 2010).

If the preamble is construed to be a claim limitation, Denney discloses it. Hale, ¶125. As described above regarding Claims 10-12, Denney discloses modifying codons to prepare vectors that contain codon optimized DNA sequences. *Id*. Denney states that it provides "improved methods for the amplification and expression of recombinant genes in cells" and that its methods "permit the efficient isolation of the desired amplified cell lines with a considerable savings in time relative to existing amplification protocols." Denney, ¶2, 17, 370; Hale, *id*. Denney explains that this improved expression is achieved through modifying (optimizing) codons, citing Jurgen Haas et al., *Codon usage limitation in the expression of HIV-1 envelope glycoprotein,* 2 Current Biology 315 (1996) (Ex1032) and Sergei Zolotukhin et al., *A 'Humanized' Green Fluorescent Protein cDNA Adapted for High-Level Expression in Mammalian Cells,* 70 J. Virol. 4646 (1996) (Ex.1033). Denney, ¶329.

The cited references emphasize the use of codon optimization to improve protein expression, as stated in Claim 20's preamble. Hale, ¶126. Haas states that "the results obtained here with three unrelated proteins . . . suggest that codon optimization may prove to be a **fruitful strategy for improving the expression in mammalian cells** of genes that show limited translational efficacy in their native form." Haas at 322 (emphasis added). Similarly, Zolotukhin explains that "the system described here [i.e., codon optimization] could be used for **efficient transduction and expression of genes into cells of mammalian origin**." Zolotukhin at 4654 (emphasis added).

Denney's method also meets each limitation of Claim 20 by disclosing the expression, amplification and isolation of the claimed immunoglobulins in mammalian cells. Hale, ¶127. Denney discloses limitation (a):

> "*a) transfecting a mammalian cell with a nucleic acid encoding an immunoglobulin heavy chain,*
>
> > *wherein the nucleic acid encoding the immunoglobulin heavy chain comprises the nucleic acid ggaaaa, or the nucleic acid ggcaaa, or the nucleic acid gggaaa, or the nucleic acid gggaag, or the nucleic acid ggcaag, or the nucleic acid gggaag encoding the glycine-lysine-dipeptide contained in the C_H3- or C_H4-domain of the immunoglobulin heavy chain"*

Denney discloses that "[p]lasmids encoding the chimeric heavy and light chains derived from the patient's Ig are electroporated . . . into BW5147.G.1.4 cells. . . " *See* Denney, ¶358. Electroporation is a standard method for

transfecting cells and BW5147.g.1.4 cells are **mammalian**. Denney, ¶159; Hale, ¶129. As described above regarding Claims 1 and 10, these plasmids comprise the nucleic acid "**ggcaag**" encoding the glycine-lysine dipeptide in the heavy chain C_H3-domain. Denney, ¶329 and SEQ ID NOs:44 and 46; Hale, *id*.

Denney's method also meets limitation (b):

> *"b) cultivating the transfected mammalian cell under conditions suitable for the expression of the immunoglobulin"*

Hale, ¶130.

Under "Expression and Amplification of Tumor-Specific Ig in Mammalian Cells", Denney discloses that the transfected mammalian cells "are then grown in selective medium followed by growth in medium containing MTX as described in Examples 7 and 8." *See* Denney, ¶358, 276-305. Ultimately "[t]he tumor-specific Ig [was] **expressed** by the amplified cell lines . . ." *See* Denney, ¶360; Hale, ¶131.

Finally, Denney's method meets limitation (c):

> *"c) recovering the immunoglobulin from the culture or the cell."*

Hale, ¶132.

Under "Purification of Tumor-Specific Ig From Amplified Cell Lines", Denney states that "[t]he tumor-specific Ig expressed by the amplified cell lines . . . is purified by chromatography of culture supernatants on Protein G Sepharose." Denney, ¶360. Purification by chromatography on Protein G Sepharose is a

standard method for **recovering** an immunoglobulin from a cell culture. Hale, ¶133.

Thus, Denney anticipates Claim 20.

ix. *In the Alternative, Denney Renders the Challenged Claims Obvious*

For the reasons described above, Denney anticipates Claims 1-3, 5, 10-12 and 20. Hale, ¶135. To the extent Denney is not found to anticipate any Challenged Claim, these claims are unpatentable under § 103(a) as obvious over Denney. *Cohesive Techs.,* 543 F.3d at 1364; Hale, ¶136-38. Denney's anticipatory disclosures described above would provide a POSA ample motivation and a reasonable expectation of success to make the nucleic acids of Claims 1-3 and 5, the systems of Claims 10-12, and the method of Claim 20. *See* § X.B.i-viii, *supra*; Hale, ¶136.

Denney discloses the nucleic acid "ggcaag" encoding the glycine-lysine dipeptide in the C_H3-domain of the Ig heavy chain, as claimed in Claims 1 and 20. Hale, *id*. Denney discloses this nucleic acid in a plasmid and in an isolated CHO cell (as claimed in Claims 10-12), as well as the narrower subset of nucleic acids of Claims 2, 3 and 5. *Id*. To the extent the Board concludes that Denney does not anticipate Claim 12 because Denney did not actually prepare a plasmid in a CHO cell, it would have been obvious to prepare the plasmid in this manner based on Denney's express teaching to do so: "[a] variety of mammalian cell lines may be

employed for the expression of recombinant proteins according to the methods of the resent [sic] invention. Exemplary cell lines include **CHO cell lines** . . ." *See* Denney, ¶159 (emphasis added); *id*.

Denney also describes in detail each of the steps of Claim 20: (a) transfecting a mammalian cell with the nucleic acid "ggcaag", (b) cultivating the transfected mammalian cell, and (c) recovering the immunoglobulin. *See* § X.B.viii, *supra*; Denney, ¶276-305, 323, 355-360; Hale, ¶137. To the extent that Claim 20's preamble is construed to be a limitation (which it is not), Denney teaches modifying the codons of the native heavy chain sequence to improve immunoglobulin expression and then expressing it in mammalian cells in the claimed manner. Hale, ¶138. To the extent Denney's disclosure is not found to be anticipatory (which it is), as described above in § VI.B, skilled antibody engineers as of June 2008 were focused on optimizing expression systems to improve recombinant protein yields and would have reasonably expected that Denney's method involving mammalian cells and codon optimization would achieve this desired result. Hale, ¶125-26, 136-38. The POSA's expectation of success would be particularly reasonable in view of Denney's repeated statements that it provides "improved methods for the amplification and expression of recombinant genes in cells" (*see, e.g.,* Denney, ¶2, 15-17), and the numerous other successful examples of codon optimization in the art (reviewed, for example, in Gustafsson). *Id*.

Denney's citation to references explaining the usefulness of codon optimization for improving expression would further bolster a POSA's motivation to modify and express the nucleic acid sequences of the native heavy chain in the claimed manner and their reasonable expectation that such efforts would succeed. Denney, ¶329; Hale, ¶138.

Accordingly, should the Board determine that Claims 1-3, 5, 10-12 and 20 are not anticipated (a finding that would, in Petitioner's view, be inapposite to Denney's disclosures), Denney renders these claims obvious. Hale, *id*.

C. Ground 2: Loetscher Anticipates and/or Renders Obvious the Challenged Claims

Loetscher describes antibodies against amyloid beta 4. It provides the nucleic acid and amino acid sequences for a specific human IgG1 antibody called "Antibody A." *See* Loetscher, p. 10, 64-72; Hale, ¶85. SEQ ID NO:23 encodes the heavy chain of Antibody A and is optimized for recombinant protein production. *See* Loetscher, p. 10; Hale, ¶87.

To Petitioner's knowledge, Loetscher was not cited during prosecution.

Loetscher was published on June 21, 2007 and was publicly available more than one year before the '225 Patent's effective filing date. It is therefore § 102(b) prior art.

i. ***Loetscher Anticipates Claim 1***

Loetscher expressly discloses every requirement of Claim 1. Loetscher discloses the first limitation of Claim 1:

> *"A nucleic acid encoding the amino acid sequence of the C-terminal part of the C_H3-domain of an immunoglobulin of the class IgA or IgG, or the amino acid sequence of the C-terminal part of the C_H4-domain of an immunoglobulin of the class IgE or IgM…"*

Loetscher's SEQ ID NO:23 discloses a nucleic acid encoding the heavy chain of an IgG1 called Antibody A, including the C-terminal part of the C_H3-domain. *See* Loetscher, p. 58, 61-62; Hale, ¶141.

Loetscher discloses the sequence "**ggcaaa**" of the second limitation of Claim 1 (emphasis added):

> *"wherein the glycine-lysine-dipeptide comprised in said amino acid sequence of the C-terminal part of the C_H3- or C_H4-domain is encoded by one of the following nucleic acid sequences, ggaaca, ggcaac, gggaaa, ggaaag, ggcaag, and gggaag, the nucleic acid ggaaaa, or the nucleic acid **ggcaaa**."*

Hale, ¶142.

In Loetscher, nucleic acid SEQ ID NO:23 corresponds to amino acid SEQ ID NO:6. Loetscher, p. 7, 10-12; Hale, ¶143. The C-terminal amino acids of Loetscher's SEQ ID NO:6, with the glycine-lysine dipeptide at the end, are shown below (highlight added):

<210> 6
<211> 456
<212> PRT
<213> artificial sequence

<220>
<223> heavy chain with Fc-region of ANTIBODY A

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

The C-terminal glycine-lysine dipeptide comprised in Loetscher's amino acid SEQ ID NO:6 is encoded by "ggcaaa", which is one of the nucleic acid sequences in Claim 1. *See* Loetscher, SEQ ID NO:23, nucleotides 3976 to 3981; Hale, ¶144. The relevant portion of Loetscher's nucleic acid SEQ ID NO:23 is shown below (highlight added):

<210> 23
<211> 3984
<212> DNA
<213> artificial sequence

<220>
<223> alternative sequence encoding heavy chain with Fc-region of ANTIBODY A

<400> 23

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 3960

ctctccctgt ccccgggcaa atga 3984

Thus, Loetscher discloses all limitations of and anticipates Claim 1. *Id.*, ¶145.

ii. ***Loetscher Anticipates Dependent Claims 2-5 and 10-12***

Challenged Claims 2-5 and 10-12 were described in detail above. *See* § VII.B.ii and § X.B.ii-vii. Loetscher discloses every requirement of these claims, as follows:

Claim	***Loetscher***
2. The nucleic acid of **claim 1**, wherein said nucleic acid encodes an amino acid sequence selected from the amino acid sequences of SEQ ID NO: 1, 3, 4, 5, 6, 7, or 8	As explained above regarding Claim 1, the nucleic acid claimed in Claim 1 is disclosed in Loetscher's SEQ ID NO:23 and the corresponding amino acid sequence is Loetscher's SEQ ID NO:6. *See* Loetscher, p. 7, 10-12; Hale, ¶147. Loetscher's SEQ ID NO:6 is identical to **SEQ ID NO:5** of the '225 Patent, as shown below: > Loetscher SEQ ID NO:6 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK > '225 Patent SEQ ID NO:5 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK Hale, *id*. Thus, Loetscher anticipates Claim 2. *Id.*, ¶147-48.
3. The nucleic acid of **claim 2**, wherein the nucleic acid encoding said glycine-lysine-dipeptide is preceded by the	As described above regarding Claim 2, Loetscher's SEQ ID NO:23 discloses the nucleic acid claimed in Claim 2. Hale, ¶150. In Loetscher's SEQ ID NO:23, the nucleic acid encoding the glycine-lysine dipeptide, "ggcaaa", is preceded by the

nucleotide g or a.	nucleotide "g". The relevant portion of Loetscher's SEQ ID NO:23 is shown below ("g" highlighted in green): <210> 23 <211> 3984 <212> DNA <213> artificial sequence ctctccctgt ccccgggcaa atga *Id*. Thus, Loetscher anticipates Claim 3.
4. The nucleic acid of **claim 3,** wherein said glycine-lysine-dipeptide is encoded by the nucleic acid ggaaaa, or the nucleic acid ggcaaa, or the nucleic acid gggaaa.	As described above regarding Claim 3, Loetscher's SEQ ID NO:23 discloses the nucleic acid "**ggcaaa**" of Claim 3. Hale, ¶153. Thus, Loetscher anticipates Claim 4. *Id*., ¶154.
5. The nucleic acid of **claim 1**, wherein the C-terminal part of the C_H3 domain, or the C-terminal part of the C_H4 domain, comprises at least the 20 C-terminal amino acids of the immunoglobulin heavy chain primary amino	As explained above regarding Claim 1, Loetscher's SEQ ID NO:23 discloses the nucleic acid of Claim 1. Hale, ¶140-45. SEQ ID NO:23 encodes the entire C_H3-domain of Cγ1. *See* Loetscher, p. 10; Hale, ¶156. Loetcher's SEQ ID NO:23 therefore includes at least the 20 C-terminal amino acids of the heavy chain amino acid sequence (i.e., the final 20 amino acids at the C-terminus of the amino acid sequence) to which it

acid sequence.	corresponds, Loetscher's SEQ ID NO:6. *Id.* The image below shows the entirety of Loetscher's SEQ ID NO:6: > Loetscher SEQ ID NO:6 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP**GK** The glycine-lysine dipeptide falling at the very end of the amino acid sequence comes within the **last 20 amino acids**. Thus, Loetscher anticipates Claim 5. *Id.*
10. A plasmid comprising the nucleic acid of **claim 1**.	As explained above regarding Claim 1, the nucleic acid of Claim 1 is disclosed in Loetscher's SEQ ID NO:23. Hale, ¶140-45. Figure 1 of Loetscher includes plasmid maps of two **plasmids** comprising nucleic acids encoding Antibody A's heavy chain. *See* Loetscher, Figs. 1A and 1C, p. 64 ("Example 1.1: Vector Construction"); Hale, ¶158. Although the nucleic acids in Figure 1 may correspond to additional SEQ ID NOs, Loetscher explains that SEQ ID NO:23 may be used to construct the plasmid. Hale, ¶159. Loetscher states: "Alternatively, said heavy chain may be

	encoded by a nucleic acid sequence that is optimized for recombinant production as exemplified by the following sequence [SEQ ID NO:23].” Loetscher, p. 10; *see also* Claim 7 (“The antibody molecule of any of claims 1 to 5, wherein the variable region comprising a glycosylated asparagine (Asn) is comprised in a heavy chain selected from the group consisting of: (a) a heavy chain polypeptide encoded by a nucleic acid molecule as shown in **SEQ ID NO**S:5, **23** or 25….”), Loetscher, p. 98 (emphasis added); Hale, ¶159. Thus, Loetscher anticipates Claim 10. Hale, ¶160.
11. An isolated cell comprising the nucleic acid of **claim 1**, wherein said cell is a mammalian cell.	Loetscher’s Example 1.2 describes the transfection of **mammalian CHO cells** with vectors containing a heavy chain gene encoding Antibody A. *See* Loetscher, p. 64-65; Hale, ¶162. The transfected cells were **isolated** and shown to comprise nucleic acid encoding IgG by the fact that they expressed Antibody A. *Id*. As described above regarding Claim 10, the vector in Example 1.2 may comprise Loetscher’s nucleic acid SEQ ID NO:23, which meets the limitations of

	Claim 1 of the '225 Patent. Hale, ¶163. Loetscher discloses that, in addition to CHO cells, other mammalian cell lines may be used. *See* Loetscher, p. 33-34; Hale, ¶164. Thus, Loetscher anticipates Claim 11. Hale, ¶165.
12. The cell of **claim 11**, characterized in that said mammalian cell is selected from a CHO cell, a HEK cell, or a BHK cell.	As explained above regarding Claims 1 and 11, Loetscher discloses the cell of Claim 11. Hale, ¶146. Loetscher states that **CHO cells or HEK cells**, among others, may be used with the nucleic acids of the invention. Loetscher, p. 33-34; Hale, ¶166. Example 1.2 specifically describes the expression of Antibody A in CHO cells. *See* Loetscher, p. 64-65; Hale, ¶167. Thus, Loetscher anticipates Claim 12. Hale, *id*.

iii. ***Loetscher Anticipates Claim 20***

Loetscher expressly discloses every requirement of Claim 20 and therefore anticipates it. Hale, ¶168.

Claim 20 begins with the preamble:

"A method for improving the expression of an immunoglobulin in a mammalian cell, comprising the following steps…"

The preamble merely sets out the purpose of the alleged invention and is not a claim limitation. *See* § VIII, *supra*; Hale, ¶169. Steps (a), (b) and (c) of Claim 20 are simply the plasmid and host cells of Claims 10-12 for expression of the nucleic acid of Claim 1, all of which Loetscher discloses. *See* § X.C.i-ii, *supra*; Hale, ¶171. Loetscher therefore anticipates Claim 20. *Marrin*, 599 F.3d at 1295.

If the preamble is construed to be a claim limitation, Loetscher discloses it. Hale, ¶170. As described above regarding Claims 10-12, Loetscher discloses vectors containing DNA sequences encoding IgG. *Id.*, ¶156-67. Loetscher states that the "heavy chain may be encoded by a nucleic acid sequence that is **optimized for recombinant production** as exemplified by [SEQ ID NO:23]." Loetscher, p. 10 (emphasis added); Hale, ¶170. SEQ ID NO:23 was optimized to improve the expression of Loetscher's recombinant proteins by modifying codons away from the wild-type sequence of Loetscher's SEQ ID NO:25. *See* Loetscher, p. 10, 12; Hale, *id*. Loetscher therefore describes a product of and method for improving immunoglobulin expression in a mammalian cell. *Id.*

Loetscher's method also meets each of Claim 20's limitations by disclosing a method for expressing and then isolating the claimed immunoglobulin in a mammalian cell. *See* Loetscher, p. 35 and Examples 1-3, p. 64-72; Hale, ¶171.

Loetscher discloses limitation (a):

> "*a) transfecting a mammalian cell with a nucleic acid encoding an immunoglobulin heavy chain,*
>
> > *wherein the nucleic acid encoding the immunoglobulin heavy chain comprises the nucleic acid ggaaaa, or the nucleic acid ggcaaa, or the nucleic acid gggaaa, or the nucleic acid gggaag, or the nucleic acid ggcaag, or the nucleic acid gggaag encoding the glycine-lysine-dipeptide contained in the C_H3- or C_H4-domain of the immunoglobulin heavy chain"*

Hale, ¶172.

Under "Transfection of CHO cells and expression of ANTIBODY A", Loetscher's Example 1.2 describes how "**[mammalian] CHO K1 cells**… were **transfected** with the vector pEE14.4Mab31 containing both heavy and light chain genes by liposomal transfection…" Loetscher, p. 64-65; Hale, ¶173. As discussed above regarding Claims 1 and 10, pEE14.4Mab31 may comprise the nucleic acid "**ggcaaa**" encoding the glycine-lysine dipeptide in the heavy chain C_H3-domain. *See* Loetscher, p. 10; Hale, *id*.

Loetscher's method also meets limitation (b):

> "*b) cultivating the transfected mammalian cell under conditions suitable for the expression of the immunoglobulin"*

Hale, ¶174.

Example 2 ("Production of ANTIBODY A (by fed-batch fermentation)") details the **cultivation of the transfected mammalian CHO cells**. Loetscher, p. 66; Hale, ¶175. The conditions described are suitable for immunoglobulin

expression, as evidenced by the fact that the immunoglobulin could be recovered. *Id.*

Finally, Loetscher's method meets limitation (c):

"c) recovering the immunoglobulin from the cultures or the cell."

Hale, ¶176.

Example 3 ("Purification of ANTIBODY A") describes the **recovery** of Antibody A by purification. *See* Loetscher, p. 66-72; Hale, ¶177. "The purification process was based on three chromatographic steps and a diafiltration step," all of which were standard methods for recovering immunoglobulin from a cell culture. *Id.*

Thus, Loetscher anticipates Claim 20. Hale, ¶178.

iv. *In the Alternative, Loetscher Renders the Challenged Claims Obvious*

For the reasons described above, Loetscher anticipates Claims 1-5, 10-12 and 20. Hale, ¶179. To the extent Loetscher is not found to anticipate any Challenged Claim, these claims are unpatentable under § 103(a) as obvious over Loetscher. *Cohesive Techs.,* 543 F.3d at 1364. Loetscher's anticipatory disclosures discussed above in § X.C.i-iii would provide a POSA with ample motivation and a reasonable expectation of success to make the nucleic acids of Claims 1-5, the systems of Claims 10-12, and the method of Claim 20.

Loetscher discloses the nucleic acid "ggcaaa" encoding the glycine-lysine dipeptide in the C_H3-domain of an immunoglobulin heavy chain, as claimed in Claims 1 and 20. Hale, ¶180. Loetscher discloses this nucleic acid in a plasmid and in isolated CHO or HEK cells (as claimed in Claims 10-12), as well as the narrower subset of nucleic acids of Claims 2-5. *Id*.

Loetscher also describes in detail each of the steps of Claim 20: (a) transfecting a mammalian cell with the claimed nucleic acid "ggcaaa", (b) cultivating the transfected mammalian cell, and (c) recovering the immunoglobulin. *See* § X.C.iii, *supra*; Hale, ¶181; Loetscher, p. 64-72. To the extent the preamble is construed to be a limitation (which it is not), Loetscher teaches modifying the native heavy chain sequence to improve immunoglobulin expression and then expressing it in mammalian cells in the claimed manner. Hale, ¶182. To the extent Loetscher's disclosure is not found to be anticipatory (which it is), as described above in § VI.B, a POSA engineering therapeutic antibodies in June 2008 would have been motivated to employ Loetscher's method to improve protein expression (i.e., to ensure economy of manufacture and relative ease of purification) and would reasonably expect it to be successful. *Id*. The POSA's expectation of success would be particularly reasonable in view of Loetscher's explicit teaching that SEQ ID NO:23 was "optimized for recombinant production" and would therefore achieve this desired result. *Id.*; Loetscher, p. 10. Loetscher

also discloses the use of mammalian cells, which the POSA would recognize as a powerful technique to improve immunoglobulin expression over other expression systems. *See* § VI.B, *supra*; Loetscher, p. 64-65; Hale, *id*.

Accordingly, should the Board determine that Claims 1-5, 10-12 and 20 are not anticipated (a finding that would, in Petitioner's view, be inapposite to Loetscher's disclosures), Loetscher renders these claims obvious. Hale, ¶183.

D. Ground 3: Rosenthal Anticipates and/or Renders Obvious the Challenged Claims

Rosenthal describes monoclonal antibodies against amyloid beta. It provides the nucleic acid and amino acid sequences for a specific human IgG2 antibody called "6G". *Id.*, ¶184-85.

To Petitioner's knowledge, Rosenthal was not cited during prosecution.

Rosenthal was published on December 28, 2006 and was publicly available more than one year before the '225 Patent's effective filing date. It is therefore § 102(b) prior art.

i. *Rosenthal Anticipates Claim 1*

Rosenthal expressly discloses every requirement of Claim 1. Rosenthal discloses the first limitation of Claim 1:

> *"A nucleic acid encoding the amino acid sequence of the C-terminal part of the C_H3-domain of an immunoglobulin of the class IgA or IgG, or the amino acid sequence of the C-terminal part of the C_H4-domain of an immunoglobulin of the class IgE or IgM…"*

Hale, ¶185.

Rosenthal describes an antibody called "6G" that has a IgG2 heavy chain constant region. *See* Rosenthal, ¶250; Hale, ¶186. Rosenthal's SEQ ID NO:13 discloses the nucleic acid sequence encoding the heavy chain of 6G, including the C-terminal part of the C_H3-domain. *See* Rosenthal, ¶53, 253; Hale, *id*.

Rosenthal discloses the sequence "**ggaaag**" of the second limitation of Claim 1 (emphasis added):

> *"wherein the glycine-lysine-dipeptide comprised in said amino acid sequence of the C-terminal part of the C_H3- or C_H4-domain is encoded by one of the following nucleic acid sequences, ggaaca, ggcaac, gggaaa, **ggaaag**, ggcaag, and gggaag, the nucleic acid ggaaaa, or the nucleic acid ggcaaa."*

Hale, ¶187.

In Rosenthal, nucleic acid SEQ ID NO:13 corresponds to amino acid SEQ ID NO:11. Rosenthal, ¶53 and 253; Hale, ¶188. The C-terminal amino acids of Rosenthal's SEQ ID NO:11, with the glycine-lysine dipeptide at the end, are shown below (highlight added):

<210> SEQ ID NO 11
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 11

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

The C-terminal glycine-lysine dipeptide of Rosenthal's amino acid SEQ ID NO:11 is encoded by "ggaaag", which is one of the nucleic acid sequences claimed in Claim 1. *See* Rosenthal, SEQ ID NO:13, nucleotides 1336 to 1341; Hale, ¶189. The relevant portion of Rosenthal's nucleic acid SEQ ID NO:13 is shown below (highlight added):

<210> SEQ ID NO 13
<211> LENGTH: 1341
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 13

aacgtgttct cttgttccgt gatgcacgag gccctgcaca accactatac ccagaagagc 1320

ctgtccctgt ctccaggaaa g 1341

Thus, Rosenthal discloses all limitations of and anticipates Claim 1. Hale, ¶190.

ii. ***Rosenthal Anticipates Dependent Claims 2, 3, 5 and 10-12***

Challenged Claims 2, 3, 5, 10, 11 and 12 were described in detail above. *See* § VII.B.ii and § X.B.ii-vii. Rosenthal discloses every requirement of these claims, as follows:

Claim	***Rosenthal***
2. The nucleic acid of **claim 1**, wherein said nucleic acid encodes an amino acid	As explained above regarding Claim 1, the nucleic acid claimed in Claim 1 is disclosed in Rosenthal's SEQ ID NO:13 and the corresponding amino acid sequence is Rosenthal's SEQ ID

sequence selected from the amino acid sequences of SEQ ID NO: 1, 3, 4, 5, 6, 7, or 8	NO:11. *See* Rosenthal, ¶53, 253; Hale, ¶191-92. Rosenthal's SEQ ID NO:11 is identical to **SEQ ID NO:6** of the '225 Patent, as shown below: > ROSENTHAL SEQ ID NO:11 GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK > '225 Patent SEQ ID NO:6 GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK Hale, ¶192. Thus, Rosenthal anticipates Claim 2. *Id*.
3. The nucleic acid of **claim 2**, wherein the nucleic acid encoding said glycine-lysine-dipeptide is preceded by the nucleotide g or a.	As described above regarding Claim 2, Rosenthal's SEQ ID NO:13 discloses the nucleic acid claimed in Claim 2. Hale, ¶196. In Rosenthal's SEQ ID NO:13, the nucleic acid encoding the glycine-lysine dipeptide, "ggaaag", is preceded by the nucleotide "a". The relevant portion of Rosenthal's SEQ ID NO:13 is shown below ("a" highlighted in green): <210> SEQ ID NO 13 <211> LENGTH: 1341 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: ctgtccctgt ctccaggaaa g Thus, Rosenthal anticipates Claim 3. *Id*.

5. The nucleic acid of **claim 1**, wherein the C-terminal part of the C_H3 domain, or the C-terminal part of the C_H4 domain, comprises at least the 20 C-terminal amino acids of the immunoglobulin heavy chain primary amino acid sequence.	As explained above regarding Claim 1, Rosenthal's SEQ ID NO:13 discloses the nucleic acid of Claim 1. Hale, ¶185-190. SEQ ID NO:13 encodes the entire C_H3-domain of Cγ2. *See* Rosenthal, ¶53, 253; Hale, ¶199. Rosenthal's SEQ ID NO:13 therefore includes at least the 20 C-terminal amino acids of the heavy chain amino acid sequence (i.e., the final 20 amino acids at the C-terminus of the amino acid sequence) to which it corresponds, Rosenthal's SEQ ID NO:11. *Id.* The image below shows the entirety of Rosenthal's SEQ ID NO:11: > ROSENTHAL SEQ ID NO:11 GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP**GK** The glycine-lysine dipeptide falling at the very end of the amino acid sequences comes within the **last 20 amino acids**. *Id.* Thus, Rosenthal anticipates Claim 5. *Id*.
10. A plasmid comprising the nucleic acid of **claim 1**.	As explained above regarding Claim 1, the nucleic acid of Claim 1 is disclosed in Rosenthal's SEQ ID NO:13. Hale, ¶185-90. Rosenthal discloses plasmids comprising nucleic acid SEQ ID NO:13. *Id.*, ¶200. In Example 1, Rosenthal states: "For

	expression of full antibodies, heavy and light chain variable regions were cloned in **mammalian expression vectors** and transfected with lipofectamine into HEK 293 cells for transient expression." Rosenthal, ¶215. Rosenthal describes a plasmid called pDb.6G.hFc2α, "[which] is an expression vector comprising the heavy chain of the 6G antibody [SEQ ID NO:13], and is suitable for transient or stable expression of the heavy chain." *Id*., ¶216; Hale, ¶201. Thus, Rosenthal anticipates Claim 10. Hale, *id*.
11. An isolated cell comprising the nucleic acid of **claim 1**, wherein said cell is a mammalian cell.	As explained above regarding Claim 1, the nucleic acid of Claim 1 is disclosed in Rosenthal's SEQ ID NO:13. Hale, ¶185-90. Rosenthal discloses isolated mammalian cells comprising nucleic acid SEQ ID NO:13. Hale, ¶203-04. In Example 1, Rosenthal states: "For expression of full antibodies, heavy and light chain variable regions were cloned in mammalian expression vectors and transfected with lipofectamine into HEK 293 cells for transient expression." Rosenthal, ¶215. HEK 293 cells are **mammalian cells**. Hale, ¶203.

	Rosenthal explains that "[t]he invention also provides host cells comprising any of the polynucleotides described herein… Non-limiting examples of **<u>mammalian host cells</u>** include but not limited to COS, HeLa, and CHO cells." Rosenthal, ¶172; Hale, *id*. Thus, Rosenthal anticipates Claim 11. Hale, ¶204.
12. The cell of **claim 11**, characterized in that said mammalian cell is selected from a CHO cell, a HEK cell, or a BHK cell.	As explained above regarding Claims 1 and 11, Rosenthal discloses the cell of Claim 11. Hale, ¶202-04. Rosenthal states that **<u>CHO cells or HEK cells</u>** may be used with the nucleic acids described therein. *See* Rosenthal, ¶172, 215; Hale, ¶206. Thus, Rosenthal anticipates Claim 12. Hale, *id*.

iii. ***<u>Rosenthal Anticipates Claim 20</u>***

Rosenthal expressly discloses every requirement of Claim 20 and therefore anticipates it. Hale, ¶207.

Claim 20 begins with the preamble:

> *"A method for improving the expression of an immunoglobulin in a mammalian cell, comprising the following steps…"*

The preamble merely sets out the purpose of the alleged invention and is not a claim limitation. *See* § VIII, *supra;* Hale, ¶208. Steps (a), (b) and (c) of Claim 20 are simply the plasmid and host cells of Claims 10-12 for expression of the nucleic acid of Claim 1, all of which Rosenthal discloses. *See* § X.D.i-ii, *supra*; Hale, ¶210. Rosenthal therefore anticipates Claim 20. *Marrin*, 599 F.3d at 1295.

If the preamble is construed to be a claim limitation, Rosenthal discloses it. Hale, ¶209. Rosenthal instructs the POSA to use host cells "**capable of over-expressing**" the protein of interest, such as mammalian cells. *Id*; Rosenthal, ¶172. Rosenthal's method also used codon optimization, the well-known codon modification technique for improving immunoglobulin expression (*see, supra*, § VI.B), to develop the portion of Rosenthal's SEQ ID NO:13 that encodes the 6G heavy chain constant region. Hale, *id*. and Exhibit C. In comparison to the nucleotide sequence of a wild-type human IgG2 heavy chain constant region, the distribution of codons in Rosenthal's SEQ ID NO:13 is strongly biased towards those which are most commonly found in humans. *Id*. and ¶91. Rosenthal also explains that multiple codons can encode the same amino acid, and that "polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention." Hale, ¶209; Rosenthal, ¶164. Thus, Rosenthal's method is intended to improve protein expression, as stated in Claim 20's preamble. *Id.*

Rosenthal's method also meets each of Claim 20's limitations by disclosing a method for expressing and then isolating the claimed immunoglobulin in a mammalian cell. *See* Rosenthal, ¶26-27 and Example 1, p. 22-23; Hale, ¶210.

Rosenthal discloses limitation (a):

> "*a) transfecting a mammalian cell with a nucleic acid encoding an immunoglobulin heavy chain,*
>
> > *wherein the nucleic acid encoding the immunoglobulin heavy chain comprises the nucleic acid ggaaaa, or the nucleic acid ggcaaa, or the nucleic acid gggaaa, or the nucleic acid gggaag, or the nucleic acid ggcaag, or the nucleic acid gggaag encoding the glycine-lysine-dipeptide contained in the C_H3- or C_H4-domain of the immunoglobulin heavy chain"*

Hale, ¶211.

Example 1 of Rosenthal states that "[f]or expression of full antibodies, heavy and light chain variable regions were cloned in mammalian expression vectors and **transfected** using lipofectamine into HEK 293 cells..." Rosenthal, ¶215; Hale, ¶212. HEK 293 cells are **mammalian**. Hale, *id*. As discussed above regarding Claims 1 and 10, the vectors comprise the nucleic acid "**ggaaag**" encoding the glycine-lysine dipeptide in the heavy chain C_H3-domain. *Id*.; Rosenthal, ¶215-216, 253.

Rosenthal's method also meets limitation (b):

> "*b) cultivating the transfected mammalian cell under conditions suitable for the expression of the immunoglobulin*"

Hale, ¶213.

Rosenthal describes expression of antibody 6G, which necessarily involves cultivating the transfected cells. Hale, ¶214. Example 1 states: "For expression of full antibodies, heavy and light chain variable regions were cloned in mammalian expression vectors and transfected using lipofectamine into HEK 293 cells..." Rosenthal, ¶212. The conditions described are suitable for the expression of the immunoglobulin, as evidenced by the fact that the immunoglobulin was recovered. Hale, ¶214.

Rosenthal also discloses "a method of generating antibody 6G comprising culturing a host cell or progeny thereof under conditions that allow production of antibody 6G" and "methods of generating any of the antibodies or polypeptides described herein by **expressing** one or more polynucleotides encoding the antibody … in a suitable cell." Rosenthal, ¶26-27 (emphasis added); *see also* Claim 40; Hale, ¶214.

Finally, Rosenthal's method meets limitation (c):

"c) recovering the immunoglobulin from the cultures or the cell."

Hale, ¶215.

Example 1 states that "[a]ntibodies were purified using Protein A using standard methods." Rosenthal, ¶215; Hale, ¶216. Purification using protein A is a standard method of **recovering** immunoglobulin from a cell culture. Hale, *id*.

Rosenthal also discloses "a method of generating antibody 6G comprising culturing a host cell or progeny thereof under conditions that allow production of antibody 6G . . . and, in some embodiments, purifying the antibody 6G" and "methods of generating any of the antibodies or polypeptides described herein by expressing one or more polynucleotides encoding the antibody . . . in a suitable cell, generally followed by recovering and/or isolating the antibody or polypeptides of interest." Rosenthal, ¶26-27; *see also* Claim 40; Hale, ¶216.

Thus, Rosenthal anticipates Claim 20. Hale, ¶217.

iv. ***In the Alternative, Rosenthal Renders the Challenged Claims Obvious***

For the reasons described above, Rosenthal anticipates Claims 1-3, 5, 10-12 and 20. *Id.*, ¶218. To the extent Rosenthal is not found to anticipate any Challenged Claim, these claims are unpatentable under § 103(a) as obvious over Rosenthal. *Cohesive Techs.,* 543 F.3d at 1364. Rosenthal's anticipatory disclosures described in § X.D.i-iii would provide a POSA with ample motivation and a reasonable expectation of success to make the nucleic acids of Claims 1-5, the systems of Claims 10-12, and the method of Claim 20.

Rosenthal discloses the nucleic acid "ggaaag" encoding the glycine-lysine dipeptide in the C_H3-domain of the immunoglobulin heavy chain, as claimed in Claims 1 and 20. Hale, ¶219-20. Rosenthal discloses this nucleic acid in a

plasmid and in isolated CHO or HEK cells (as claimed in Claims 10-12), as well as the narrower subset of nucleic acids of Claims 2, 3 and 5. *Id*.

Rosenthal also describes in detail each of the steps of Claim 20: (a) transfecting a mammalian cell with the claimed nucleic acid "ggaaag", (b) cultivating the transfected mammalian cell, and (c) recovering the immunoglobulin. *See* § X.D.iii, *supra*; Rosenthal, ¶215-216, 253; Hale, ¶220. To the extent the preamble is construed to be a limitation (which it is not), Rosenthal teaches modifying the native heavy chain sequence to improve immunoglobulin expression and then expressing it in mammalian cells in the claimed manner. Hale, ¶221. To the extent that Rosenthal's disclosure is not found to be anticipatory (which it is), a POSA engineering therapeutic antibodies in June 2008 would be motivated to employ Rosenthal's method to improve protein expression and would reasonably expect it to be successful. *Id*. As described above in § VI.B, a POSA would seek to maximize protein expression (i.e., to ensure economy of manufacture and relative ease of purification), and would know that Rosenthal's method involving mammalian cells and codon optimization would likely achieve this desired result. *Id.* Such an expectation would be reinforced by Rosenthal's statement that the mammalian cells of the invention should be capable of over-expressing the nucleic acid. *Id.*; Rosenthal, ¶172.

Accordingly, should the Board determine that Claims 1-3, 5, 10-12 and 20 are not anticipated (a finding that would, in Petitioner's view, be inapposite to Rosenthal's disclosures), Rosenthal renders these claims obvious. Hale, ¶222.

E. No Objective Indicia of Non-Obviousness

No objective indicia of non-obviousness are sufficiently probative to overcome the invalidity of the '225 Patent under § 103. *Id.*, ¶224. Specifically, there are no secondary factors, such as commercial success, long-felt but unmet need, licensing, unexpected results, professional skepticism, or copying by others sufficiently probative to overcome the clear and convincing case that the Challenged Claims are invalid. *Id*.

In conclusion, the Challenged Claims are unpatentable and should be cancelled.

Date: June 14, 2018

Respectfully submitted,

/s/ Robert E. Counihan

Robert E. Counihan
USPTO Reg. No. 61,382
Jeff Oelke
USPTO Reg. No. 37,409
Vanessa Park-Thompson*
**pro hac vice admission to be sought*
White & Case LLP
1221 Avenue of the Americas
New York, New York 10020
Tel: (212) 819-8200
Fax: (212) 354-8113

rcounihan@whitecase.com
joelke@whitecase.com
vanessa.park-thompson@whitecase.com

Counsel for Pfizer Inc.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. §§ 42.24(a)(i) and 42.24(d), I hereby certify that the number of words in this Petition is 12,157, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, and appendix listing of exhibits.

Date: June 14, 2018

Signed,

/s/ Robert E. Counihan
Robert E. Counihan
USPTO Reg. No. 61,382

/s/ Jeff Oelke
Jeff Oelke
USPTO Reg. No. 37,409

/s/ Vanessa Park-Thompson
Vanessa Park-Thompson*
* *pro hac vice admission to be sought*

Counsel for Pfizer Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6 and 42.105, I hereby certify that on this 14th day of June, 2018, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,314,225 and accompanying exhibits referenced therein were served via PRIORITY MAIL EXPRESS® for single-day overnight delivery on the Patent Owner at the following correspondence address of record in PAIR:

Hoffmann-La Roche Inc.
Overlook at Great Notch
150 Clove Road
8th Floor, Suite 8 – Legal Department
Little Falls, NJ 07424

The foregoing Petition and accompanying exhibits referenced therein were also served on this 14th day of June, 2018 via PRIORITY MAIL EXPRESS® for overnight delivery on the Patent Owner at an address known to the Petitioner as likely to affect service.

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

Date: June 14, 2018

Signed,

/s/ Robert E. Counihan
Robert E. Counihan
USPTO Reg. No. 61,382

Counsel for Pfizer Inc.