Filed on behalf of Phigenix, Inc.
By: Ping Wang, M.D., Esq.
Gregory Porter, Esq.
Michael Ye, Ph.D., Esq.
ANDREWS KURTH, LLP
1350 I Street, NW
Suite 1100
Washington, D.C. 20005
Tel.: (202) 662-2700
Fax: (202) 662-2739
Email: PingWang@AndrewsKurth.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PHIGENIX, INC.
Petitioner
v.
IMMUNOGEN, INC.
Patent Owner of
U.S. Patent No. 8,337,856 to Walter Blättler, *et al.*
Issued on December 25, 2012
Appl. No. 11/949,351 filed on December 3, 2007

IPR Trial No. IPR2014-00676

CORRECTED PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,337,856 PURSUANT TO 35 U.S.C. §312 AND 37 C.F.R. §42.108

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EXHIBIT LIST

Exhibit No.	Description	Issue or Publication Date
1001	U.S. Patent No. 8,337,856 (Blättler, *et al.*)	December 25, 2012
1002	Slamon, *et al.*, "Studies of the HER-2/*neu* proto-oncogene in human breast and ovarian cancer." *Science* 244:707-712 (1989).	May, 1989
1003	Press, *et al.*, "HER-2/*neu* gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas." *J. Clin. Oncol.* 15:2894-2904 (1997).	August, 1997
1004	Phillips, *et al.*, "Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate." *Cancer Res.* 68: 9280-9290 (2008).	November 15, 2008
1005	Hudziak, *et al.*, "p185^{HER2} monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor." *Mol. Cell. Biol.*, 9:1165-1172 (1989).	March, 1989
1006	McKenzie, *et al.*, "Generation and characterization of monoclonal antibodies specific for the human *neu* oncogene product, p185." *Oncogene*, 4:543-548 (1989).	May, 1989
1007	Ring, *et al.*, "Identity of BCA200 and c-erbB-2 indicated by reactivity of monoclonal antibodies with recombinant c-erbB-2." *Mol. Immunol.*, 28: 915-917 (1991).	August, 1991
1008	HERCEPTIN® Label	September, 1998
1009	Blythman, *et al.*, "Immunotoxins: hybrid molecules of monoclonal antibodies and a toxin subunit specifically kill tumour cells." *Nature*, 290:145-146 (1981).	March 12, 1981

1010	Vitetta, *et al.*, "Monoclonal antibodies as agonists: an expanded role for their use in cancer therapy." *Cancer Res.*, 54:5301-5309 (1994).	October 15, 1994
1011	Maier, *et al.*, "Requirements for the internalization of a murine monoclonal antibody directed against the HER-2/*neu* gene product c-*erbB-2*." *Cancer Res.*, 51: 5361-5369 (1991).	October 1, 1991
1012	Chari, *et al.*, "Immunoconjugates containing novel maytansinoids: promising anticancer drugs." *Cancer Res.*, 52:127-131 (1992).	January 1, 1992
1013	Batra, *et al.*, "Recombinant anti-erbB2 immunotoxins containing *Pseudomonas* exotoxin." *Proc. Natl. Acad. Sci., USA*, 89:5867-5871 (1992).	July, 1992
1014	Liu, *et al.*, "The development of antibody delivery systems to target cancer with highly potent maytansinoids." *Exp. Opin. Invest. Drugs*, 6:169-172 (1997).	February, 1997
1015	Chari, "Targeted delivery of chemotherapeutics: tumor-activated prodrug therapy." *Adv. Drug Del. Rev.*, 31: 89-104 (1998).	January 1, 1998
1016	Declaration of Michael G. Rosenblum, Ph.D.	
1017	U.S. Patent No. 5,770,195 (Hudziak, *et al.*)	June 23, 1998
1018	Rosenblum, *et al.*, "Recombinant immunotoxins directed against the *c-erbB-2/HER2/neu* oncogene product: *in vitro* cytotoxicity, pharmacokinetics, and *in vivo* efficacy studies in xenograft models." *Clin. Cancer Res.*, 5:865-874 (1999).	April, 1999
1019	Baselga, *et al.*, "Recombinant humanized anti-HER2 antibody (Herceptin™) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/*neu* overexpressing human breast cancer xenografts." *Cancer Res.*, 58:2825-2831, (1998).	July 1, 1998
1020	Pegram, *et al.*, "Inhibitory effects of combinations of HER-2/*neu* antibody and chemotherapeutic agents used for treatment of human breast cancers." *Oncogene*, 18:2241-2251 (1999).	April 1, 1999

1021	Morgan, *et al.*, "Immunotoxins of *Pseudomonas* exotoxin A (PE): effect of linkage on conjugate yield, potency, selectivity and toxicity." *Mol. Immunol.* 27:273-282 (1990).	March, 1990
1022	Carter, *et al.*, "Humanization of an anti-p185^{HER2} antibody for human cancer therapy." *Proc. Natl. Acad. Sci., USA*, 89:4285-4289 (1992).	May, 1992
1023	Liu, *et al.*, "Eradication of large colon tumor xenografts by targeted delivery of maytansinoids." *Proc. Natl. Acad. Sci., USA*, 93:8618-8623 (1996).	August, 1996
1024	U.S. Patent No. 5,208,020 (Chari, *et al.*)	May 4, 1993
1025	Cohen, "Treatment With Anti-ErbB2 Antibodies," U.S. Pre-Grant Publication No. 2003/0170235.	September 11, 2003*
1026	Declaration of Walter Blättler and Ravi Chari filed on September 11, 2012, in U.S. Application No. 11/949,351.	September 11, 2012
1027	Response to Office Action of June 8, 2010, filed on July 6, 2010, in U.S. Application No. 11/949,351.	July 6, 2010
1028	Declaration by Mark X. Sliwokoswki, Ph.D. , filed on July 6, 2010, in U.S. Application No. 11/949,351.	July 6, 2010
1029	Declaration by Barbara Klencke, M.D. , filed on July 6, 2010, in U.S. Application No. 11/949,351.	July 6, 2010
1030	Suzuki, *et al.*, "Immunoselective cell growth inhibition by antibody-Adriamycin conjugates targeting c-*erb*B2 product on human cancer cells." *Biol. Pharm. Bull.* 18:1279-1282 (1995).	September, 1995
1031	Drewinko, *et al.*, "Differential killing efficacy of twenty antitumor drugs on proliferating and nonproliferating human tumor cells." *Cancer Res.* 41:2328-2333 (1981).	June, 1981
1032	*Curriculum vitae* of Michael G. Rosenblum, Ph.D.	

*** Priority to May 14, 1999**

PETITION FOR *INTER PARTES* REVIEW OF U.S. PAT. NO. 8,337,856

I. INTRODUCTION

Phigenix Inc. ("Petitioner") hereby requests *Inter Partes* Review (IPR) of Claims 1-8 ("challenged claims") of U.S. Patent 8,337,856 ("the '856 patent", **Ex. 1001**) pursuant to 35 U.S.C. § 311 and 37 C.F.R. §§ 42.1 *et seq.*

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies that the '856 patent, which issued on December 25, 2012, is available for IPR and that Petitioner is not barred or estopped from requesting an IPR for the challenged claims of the '856 patent.

III. MANDATORY REQUIREMENTS, NOTICES AND FEES

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

Petitioner Phigenix is the sole real party-in-interest.

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

To the best of Petitioner's knowledge, there are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

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

LEAD COUNSEL	BACK-UP COUNSEL
Ping Wang, M.D., Esq., Reg. No. 48,328 Andrews Kurth, LLP 1350 I Street NW, Suite 1100 Washington, D.C. 20005 Phone No. (202) 662-3042 Fax No. (202) 662-3729 Email: PingWang@andrewskurth.com	**Gregory Porter, Esq., Reg. No. 40,131** Andrews Kurth, LLP 600 Travis, Suite 4200 Houston, TX 77002 Phone No. (713) 220-4621 Fax No. (713) 220-4257 Email: GregPorter@andrewskurth.com

Please address all papers concerning this matter to lead counsel and back-up counsel at the above addresses.

D. Power of Attorney (37 C.F.R. §42.10(b))

A Power of Attorney is submitted herewith pursuant to 37 C.F.R. §42.10(b).

E. Petition Fees (35 U.S.C. § 312(1) and 37 C.F.R. § 42.15)

The Director is authorized to charge the fee specified by 37 C.F.R. § 42.15(a) to Deposit Account No. 50-2849.

F. Proof of Service (37 C.F.R. §§ 42.6(e) and 42.105(a))

Proof of service is provided herein at the end of this Petition.

IV. STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.22(a)(1)

The Petitioner requests *Inter Partes* Review under 37 C.F.R. § 42.108 as to Claims 1-8 of the '856 patent and a ruling that Claims 1-8 of the '856 patent are unpatentable based on one or more of the grounds under 35 U.S.C. § 103 for the reasons set forth herein. Petitioner's detailed statement of the reasons for the relief requested is set forth in Section VI below.

V. RELEVANT INFORMATION CONCERNING THE CONTESTED PATENT

A. The '856 Patent

The '856 Patent was filed as US Patent Application Serial No. 11/949,351 on December 3, 2007, which is a divisional application of US Patent Application No. 11/488,545, filed on July 17, 2006, now US Patent No. 7,575,748, which is a continuation application of US Patent Application No. 09/811,123, filed on March 16, 2001, now US Patent No. 7,097,840, which claims priority from Provisional Application Nos. 60/238,327, filed on October 5, 2000, 60/189,844, filed on March 16, 2000 and 60/327,563, filed on June 23, 2000.

The '856 patent purports to provide a "novel" composition comprising an anti-ErbB receptor antibody-maytansinoid conjugate. Independent Claim 1 of the '856 patent recites an immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8. Dependent

Claims 2-8 further recite the structure of the immunoconjugate and a pharmaceutical composition comprising the immunoconjugate ('856 patent, **Ex. 1001**).

B. Technical Background

The best known anti-ErbB2 antibody, trastuzumab (HERCEPTIN®), targets the extracellular domain of the ErbB2 receptor and was approved by the FDA in 1998 for treatment of patients with metastatic breast cancer whose tumors overexpress the ErbB2 receptor protein (HERCEPTIN® Label, **Ex. 1008**).

ErbB2 (HER2) is a membrane-bound receptor tyrosine kinase that plays critical roles in cancer development. Amplification and overexpression of ErbB2 occur in 25-30% of human breast cancer and are predictive of poor clinical outcome (Slamon, *et al.*, *Science*, 244:707-712 (1989), **Ex. 1002**; Press, *et al.*, *J. Clin. Oncol.* 15: 2894-2904 (1997), **Ex. 1003**). ErbB2 is an ideal target for antibody-targeted drug delivery because it is highly differentially expressed on breast tumor cells (1-2 million copies per cell) compared with normal epithelial cells (Phillips, *et al.*, *Cancer Res.* 68:9280-9290 (2008), **Ex. 1004**, page 9281, left col., 1st para.).

Specific targeting of ErbB2 overexpressing tumors can be accomplished with antibodies directed against the extracellular domain of the ErbB2 receptor.

A number of anti-ErbB2 antibodies have been developed and tested in animal models for their efficacy in inhibiting tumor growth (Hudziak, *et al.*, *Mol. Cell. Biol.* 9:1165-1172 (1989), **Ex. 1005**; McKenzie, *et al. Oncogene* 4:543-548 (1989), **Ex. 1006**; and Ring, *et al.*, *Mol. Immun.* 28:915-917 (1991), **Ex. 1007**).

The cytotoxicity of an antibody may be enhanced by conjugating the antibody to another cytotoxic agent, such as a chemotherapy drug, to form an immunoconjugate to kill a targeted cancer cell. The concept of using "immunoconjugates" or "immunotoxins" for killing cancer cells has been around for more than 30 years (Blythman, *et al.*, *Nature* 290:145-146 (1981), **Ex. 1009**; Vitetta, *et al.*, *Cancer Res.*, 54:5301-5309, (1994); **Ex. 1010**).

Following the discovery of the correlation between ErbB2/HER2 overexpression and breast cancer, a number of independent investigators created immunoconjugates targeting the ErbB2 receptor (Maier, *et al.*, *Cancer Res.*, 51:5361-5369 (1991) ("Maier 1991"), **Ex. 1011**; Chari, *et al.*, *Cancer Res.* 52:127-131 (1992) ("Chari 1992"), **Ex. 1012**; Batra, *et al.*, *Proc. Natl. Acad. Sci., USA* 89: 5867-5871 (July 1992) ("Batra 1992"), **Ex. 1013**). Batra 1992 describes a number of anti-ErbB2 immunoconjugates containing different anti-ErbB2 monoclonal antibodies linked to a *Pseudomonas* exotoxin. Maier 1991 and Chari 1992 describe anti-ErB2 immunoconjugates containing the anti-ErbB2 monoclonal antibody TA.1 linked to the ricin toxin and the maytansine toxin,

respectively. All of the above-described ErbB2-targeted immunoconjugates were found to selectively kill cells overexpressing ErbB2 (**Ex. 1011**, p. 5364, left column; **Ex. 1012**, p. 129, left column).

Maytansine is a highly cytotoxic drug that kills cells by interfering with the formation of microtubules and depolymerization of already formed microtubules. Maytansine is about 100- to 1000-fold more toxic for a range of human cancer cell lines than are most other anticancer drugs (**Ex. 1012**). Because of its potency and activity against microtubule polymerization, maytansine and maytansinoid derivatives are particularly attractive cytotoxic agents for use in antibody-drug therapy (**Ex. 1012**; Liu, *et al.*, *Exp. Opin. Invest. Drugs*, 6:169-172 (1997) ("Liu 1997"), **Ex. 1014**; Chari, *Adv. Drug. Del.* Rev., 31:89-104 (1998) ("Chari 1998"), **Ex. 1015**).

C. Ordinarily Skilled Artisan (Person of Ordinary Skill in the Art)

An ordinarily skilled artisan is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '856 patent, an ordinarily skilled artisan would have had knowledge of the scientific literature concerning pharmaceutical compositions for the treatment of breast cancer as of 2000. An ordinarily skilled artisan would be a person having an M.D. degree, and/or a Ph.D. degree in a Chemistry-, Pharmacology-, or Biology-related field, and at least five years of

experience working with antibodies and immunoconjugates. An individual with such credentials and experience as of March, 2000, would be well versed in techniques for producing immunoconjugates, as well as methods for testing the immunoconjugates in *in vitro* and *in vivo* systems (Rosenblum Declaration, **Ex. 1016**, para. 7). Such a skilled artisan would have substantial familiarity, training or experience with compositions for the treatment of breast cancer.

D. Construction of Terms Used in the Claims

Petitioner submits that the terms recited in the claims of the '856 patent are to be given their broadest reasonable interpretation in light of the specification (37 C.F.R. §42.100(b)). Petitioner respectfully submits that the specification of the '856 patent defines a pharmaceutically-acceptable carrier as including "bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution" (**Ex. 1001**, col. 42, lines 4-9). Petitioner further submits that the remainder of the terms recited in the claims of the '856 patent are to be given their ordinary and customary meaning known in the art.

VI. IDENTIFICATION OF CHALLENGE (37 C.F.R. §42.104(b))

Inter Partes Review of Claims 1-8 of the '856 patent (**Ex. 1001**) is requested on the grounds for unpatentability listed in the chart below. Per

37 C.F.R. §42.6(d), copies of the prior art references, as well as other references cited herein are filed herewith as **Exhibits 1002-1032**. In support of the proposed grounds for unpatentability, this petition is accompanied by the Declaration of Michael G. Rosenblum, Ph.D., a technical expert, (**Ex. 1016**), which explains what the art would have conveyed to a person of ordinary skill in the art.

Ground	Claim(s)	Basis for Unpatentability
1	1-8	Obvious (§103) over Chari 1992 in view of HERCEPTIN® Label
2	1-8	Obvious (§103) over Chari 1992 and HERCEPTIN® Label, further in view of Hudziak 1998 and/or Rosenblum 1999
3	1-8	Obvious (§103) over Chari 1992 and HERCEPTIN® Label, further in view of Hudziak 1998 and/or Rosenblum 1999, and further in view of Baselga 1998 and/or Pegram 1999
4	6, 8	Obvious (§103) over Chari 1992 and HERCEPTIN® Label and further in view of Morgan 1990
5	1-8	Obvious (§103) over Chari 1992 and Carter 1992 and common knowledge in the art
6	1-5, 7	Obvious (§103) over Liu 1996 in view of HERCEPTIN® Label
7	6, 8	Obvious (§103) over Liu 1996 in view of HERCEPTIN® Label and further in view of Morgan 1990
8	1-8	Obvious (§103) over Cohen 1999 in view of Chari 1992

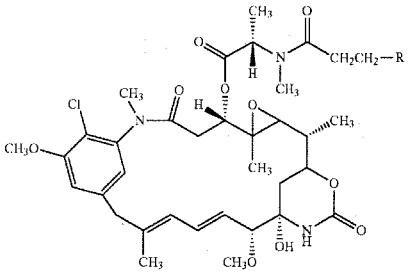
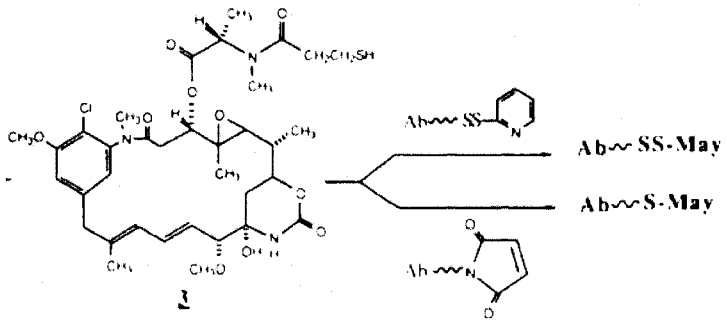
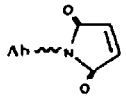
A. Ground 1: Claims 1-8 Are Obvious Over Chari 1992 In View Of HERCEPTIN® Label

Chari 1992 (**Ex. 1012**) was published on January 1, 1992, more than a year before the earliest effective filing date of the '856 patent. HERCEPTIN® Label (**Ex. 1008**) was published in September 1998, more than a year before the earliest

effective filing date of the '856 patent. As detailed in **Table 1**, the combination of Chari 1992 and HERCEPTIN® Label teaches or suggests each and every limitation recited in Claims 1-8.

Table 1

Claims	**Disclosure of Chari 1992 and HERCEPTIN® Label**
1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8.	"We therefore prepared antibody conjugates of the maytansinoid 3 and the murine monoclonal antibody TA.1 (Fig. 2), using linkers containing either a disulfide bond or a noncleavable thioether bond. The TA.1 antibody binds to the HER-2/neu oncogene protein (also known as c-erb-2) that is expressed at high levels on human breast tumor cells (17)" (**Ex. 1012**, abridging paragraph between p. 128 and p.129) "**HERCEPTIN® (Trastuzumab)** is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd=5nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2" (**Ex. 1008**, p. 1, top left col.) **HERCEPTIN® is synonymous with huMAb4D5-8** "antibody 4D5 was humanized ....The humanized version designated HERCEPTIN® (huMAb4D5-8, rhuMAb HER2, U.S. Pat. No. 5,821,337) was tested in breast cancer patients whose tumors overexpress HER2 but who had progressed after conventional chemotherapy..." (**Ex. 1001**, col. 3, lines 10-16)

2. The immunoconjugate of claim 1, wherein the maytansinoid is DM1 having the structure:  and wherein the antibody is chemically linked to the maytansinoid via a disulfide or thioether group at "R" shown in the structure.	"We therefore prepared antibody conjugates of the maytansinoid 3 and the murine monoclonal antibody TA.1 (Fig. 2), using linkers containing either a **disulfide bond** or a noncleavable **thioether bond**" (**Ex. 1012**, abridging para. between p.128 and p. 129)  Fig. 2 of Chari 1992 (see above) shows maytansinoids and their conjugation to antibodies (**Ex. 1012**, p. 128, right col.). Compound 3 is DM1, which reacts with linker modified antibody (Ab) (or ) via the -SH group (which corresponds to the "R" group in Claim 2) to form the immunoconjugate Ab~SS-May or Ab~S-May (Fig. 2).
3. The immunoconjugate of claim 1, wherein the immunoconjugate comprises from 3 to 5 maytansinoid molecules per antibody molecule.	Chari 1992 teaches the TA.1(-SS-May)$_n$ conjugates, where n is an average number of maytansinoid molecules per antibody and where n can be 4 (**Ex. 1012**, p. 129. Table 2)
4. The immunoconjugate of claim 1, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from **N-succinimidyl-3-(2-**	" In order to generate antibody-drug conjugates the antibody was modified with **SPDP [*N*-succinimidyl-3-(2-pyridyldithio)-propionate]** to introduce dithio-pyridyl groups, **or** with **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2 was reduced to May-SH 3 (see "Materials

pyridyldithio) propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and **succinimidyl-4-(N-maleimidomethyl)cyclohexanel-1-carboxylate**.	and Methods") and reacted with the modified antibodies."(**Ex. 1012** p. 128, bottom right col. Legend of Fig. 2)
5. A pharmaceutical composition comprising an immunoconjugate of any of claims 1 to 4, and a pharmaceutically acceptable carrier.	"Each vial of HERCEPTIN® contains 440mg Trastuzumab, 9.9mg L-histidineHCl, 6.4mg L-histidine, 400mg α,α-trehalose dihydrate, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection,...." (**Ex. 1008**, p. 1, top left col.)
6. The immunoconjugate of claim 4, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"In order to generate antibody-drug conjugates the antibody was modified ... with **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2 was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies" (**Ex. 1012**, p. 128, Legend of Fig.2)
7. The immunoconjugate of claim 2, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from N-succinimidyl-3-(2-pyridyldithio)propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	" In order to generate antibody-drug conjugates the antibody was modified with **SPDP [*N*-succinimidyl-3-(2-pyridyldithio)-propionate]** to introduce dithio-pyridyl groups, or with **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2 was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies" (**Ex. 1012**, p. 128, Legend of Fig.2)

8. The immunoconjugate of claim 7, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"In order to generate antibody-drug conjugates the antibody was modified with … **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies. (**Ex. 1012**, p. 128, Legend of Fig. 2)

Intended use of a composition does not render the composition nonobvious

Claims 1-8 are directed to an immunoconjugate comprising huMAb4D5-8 conjugated to a maytansinoid. It is well established in patent law that intended use of a composition does not, in and of itself, render the composition nonobvious (see *e.g.*, *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) "Products of identical chemical composition cannot have mutually exclusive properties," and *In re Zierden*, 411 F.2d 1325, 1328 (CCPA 1969) "A mere statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable").

Chari 1992 and HERCEPTIN® Label teach every and each limitation of Claims 1-8 of the '856 patent

As shown in **Table 1** above, Chari 1992 discloses an immunoconjugate comprising a maytansinoid chemically linked to an anti-ErbB2-antibody (**Ex. 1012**, Fig. 2). Chari 1992 also discloses that the maytansinoid is DM1and that the antibody is chemically linked to the maytansinoid via a disulfide or thioether

group at the "R" position (**Ex. 1012**, Fig. 2), as recited in Claim 2 of the '856 patent. The immunoconjugate of Chari 1992 may comprise from 3-5 maytansinoid molecules per antibody molecule (**Ex. 1012**, p. 129, bottom right col. Table 2), as recited in Claim 3 of the '856 patent. The antibody and the maytansinoid were conjugated by a chemical linker selected from SPDP or SMCC (**Ex. 1012**, p. 128, bottom right col., Fig. 2), as recited in Claims 4 and 6-8 of the '856 patent.

Chari 1992 does not explicitly disclose huMAB4D5-8 (recited in Claim 1 of the '856 patent) or a pharmaceutically acceptable carrier (recited in Claim 5 of the '856 patent). However, HERCEPTIN® Label describes the clinical use of huMAB4D5-8 (*i.e.,* HERCEPTIN®), which is described as being indicated for the treatment of patients with metastatic breast cancer (**Ex. 1008**, p. 1, right col.). HERCEPTIN® Label also describes the injection of HERCEPTIN® with a pharmaceutically acceptable carrier (Bacteriostatic Water for Injection, **Ex. 1008**, p. 1, left col.).

As detailed below and confirmed by the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 12-15), Chari 1992 teaches that the anti-ErbB2 antibody-maytansinoid conjugates exhibited high antigen-specific cytotoxicity for cultured human breast cancer cells, low systemic toxicity in mice, and good pharmacokinetic behavior (**Ex. 1012**, Abstract). It would be obvious to an

ordinarily skilled artisan, at the time the '856 patent was filed, to simply substitute the mouse mAb TA.1 in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8 to produce a maytansinoid-huMAB4D5-8 conjugate based on the teachings of Chari 1992 and HERCEPTIN® Label, as well as the general knowledge in the art at that time. As noted by the Federal Circuit, combination of known elements would have been *prima facie* obvious if an ordinarily skilled artisan would have recognized an apparent reason to combine those elements and would have known how to do so (*Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1350 (Fed. Cir. 2009)).

Reason to Combine and Reasonable Expectation of Success

As described in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 12-15), an ordinarily skilled artisan would be motivated to substitute the mouse mAb TA.1 in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8 because:

(1) It was well known in the art at the time of the priority date of the '856 patent that humanized mAbs, such as huMAB4D5-8, were preferred over their mouse-derived counterparts for clinical applications, since humanized mAbs exhibit reduced immunogenicity. For example, Chari 1992 teaches that "[t]he development of 'humanized' antibodies will offer an opportunity to produce drug

conjugates that would be less immunogenic than similar conjugates of murine antibodies" (**Ex. 1012**, p. 130, bottom left col.);

(2) huMAB4D5-8 selectively binds with high affinity to HER2 and has been approved for use in humans (**Ex. 1008**, p. 1, left col.); and

(3) clinical studies indicated that huMAB4D5-8 works well in combination with microtubule-directed chemotherapy agents for the treatment of breast cancer (**Ex. 1008**, p. 1, left col.).

Substituting a mouse anti-ErbB2 antibody in an immunoconjugate with a humanized anti-ErbB2 antibody is no more than a simple substitution of one known element for another to obtain a predictable result, reduced immunogenicity for a human subject. Therefore, it would have been obvious to an ordinarily skilled artisan to apply a known technique (humanizing mouse antibody) to a known product (anti-ErbB2 antibody-maytansinoid conjugate) (**Ex. 1016**, para. 13).

Based on the detailed description in Chari 1992 and the general knowledge in the art about conjugation of maytansinoids with antibodies, an ordinarily skilled artisan would have known how to substitute the mouse mAb TA.1 in the immunoconjugate of Chari 1992 with huMAB4D5-8 to produce an immunoconjugate of maytansinoid and huMAB4D5-8. As confirmed by the Declaration of Dr. Rosenblum, maytansinoid-huMAB4D5-8 conjugate can be

produced using a conjugation process described in Chari 1992 (**Ex. 1016**, para. 14).

In addition, there would have been a reasonable expectation of success for an immunoconjugate comprising huMAB4D5-8 conjugated to a microtubule-targeting drug, such as maytansinoid, because:

(1) huMAB4D5-8 is more effective in treating breast cancer when used in combination with the microtubule targeting drug paclitaxel as described in HERCEPTIN® Label (**Ex. 1008**, p.1, left col.);

(2) Chari 1992's maytansinoid conjugates are capable of targeting the same cells as huMAB4D5-8 to deliver a more cytotoxic microtubule targeting drug, DM1, than any anticancer drug that was in clinical use at that time (**Ex. 1012**); and

(3) An immunoconjugate containing a "humanized" antibody is less immunogenic than an immunoconjugate containing a mouse antibody and renders the antibody-maytansinoid immunoconjugate more effective in humans (**Ex. 1012**; p. 130, left col.).

As noted in the MPEP, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their

combination (MPEP 2144 (II)). In the instant case, there was clearly a recognition that some advantage or expected beneficial result (*e.g.*, less immunogenicity, better targeting, and additive effect) would have been produced by the combination of Chari 1992 and HERCEPTIN® Label, based on established scientific principles at the time of the priority date of the '856 patent (*i.e*, humanized antibody is less immunogenic than mouse antibody in human patients).

B. Ground 2: Claims 1-8 Are Obvious Based on Chari 1992 In View Of HERCEPTIN® Label, Further In View Of Hudziak 1998 And/Or Rosenblum 1999

As described in Ground 1 above, Chari 1992 and HERCEPTIN® Label teach or suggest in combination each and every limitation recited in Claims 1-8 of the '856 patent. Hudziak 1998 (**Ex. 1017**) and Rosenblum 1999 (**Ex. 1018**) provide further motivation and expectation of success for modifying the TA.1-maytansinoid conjugate with huMAB4D5-8 to form huMAB4D5-8-maytansinoid conjugate as suggested by the combined teachings of Chari 1992 and HERCEPTIN® Label, as noted in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 16-18).

In particular, Hudziak 1998 discloses a method for treating breast tumor cells with an anti-HER2 4D5 monoclonal antibody (**Ex. 1017**, col. 18, lines 51-57), preferably a humanized derivative thereof (**Ex. 1017**, claims 9-12). Hudziak

1998 discloses that by inhibiting HER2 function, cell growth is inhibited and the cells are rendered more susceptible to cytotoxic factors such as the antimicrotubule drug, vinblastine (**Ex. 1017**, col. 5, lines 10-12, col. 6, lines 60-65). Hudziak 1998 thus teaches a method to inhibit ErbB2 receptor function and sensitize the tumor cells to increased cell death by administering an anti-HER2 antibody in combination with a chemotherapeutic agent, such as the antimicrotubule drug vinblastine (**Ex. 1017**, Claims 14, 23, 25, 27, 28 and 36). Hudziak 1998 further teaches that the anti-HER2 antibody may be conjugated to a chemotherapeutic agent, such as the antimicrotubule drug vinblastine (**Ex. 1017**, col. 9, lines 50-63; col. 6, lines 60-66), and used in a method for inhibiting the growth of tumor cells that overexpress HER2 receptor (**Ex. 1017**, Claim 2).

Rosenblum 1999 describes an immunotoxin (*i.e.,* immunoconjugate) comprising a humanized monoclonal antibody directed against the extracellular domain of ErbB2 (BACH-250) chemically conjugated to the ribosome-inhibiting plant toxin gelonin (rGel). Rosenblum 1999's BACH-250 immunoconjugate was internalized efficiently in the SKBR-3 breast cancer cell line, the same cells responsive to HERCEPTIN® (**Ex. 1018**, paragraph abridging pp. 868-869). In addition, of the six different cell lines expressing various levels of the ErbB2 receptor, the cytotoxic activity of the BACH-250 immunoconjugate was highest against the SKBR-3 cell line (**Ex. 1018**, p. 869, left col.). *In vivo* studies utilized

a tumor cell line (SKOV-3) overexpressing ErbB2/HER-2 at levels that may approximate those found in patients with HER2 overexpression tumors. Under these circumstances, the immunotoxin was found to have impressive antitumor effects as compared with the tumor growth behavior seen in the control groups in both the subcutaneous (*s.c.*) tumor model and the intraperitoeneal (*i.p.*) tumor model (**Ex. 1018**, Abstract, p. 871, bottom right col., and Figs. 12, 13). In particular, in athymic mice bearing *s.c.* or *i.p.* SKOV-3 tumors, immunotoxin treatment of the corresponding mouse Ab derived immunoconjugate slowed tumor growth by 99 and 94% at days 35 and 49 after implantation, respectively, and lengthened the median survival by 40% (from 30 to 50 days) in mice bearing lethal *i.p.* tumors. (**Ex. 1018**, Abstract, Figs. 12 and 13).

Reason to Combine and Reasonable Expectation of Success

As discussed above, Hudziak 1998 teaches the use of a human ErbB2 extracellular domain-targeted 4D5 monoclonal antibody (like HERCEPTIN®) in an immunoconjugate in combination with an antimicrotubule drug. Rosenblum 1999 teaches the use, efficacy and safety of an immunotoxin having humanized ErbB2 extracellular domain-targeted monoclonal antibody chemically linked to a cytotoxic moiety. These teachings provide further motivation for an ordinarily skilled artisan to substitute the anti-ErbB2 mouse mAb in the immunoconjugate of Chari 1992 with the humanized anti-ErbB2 mAb described in the

HERCEPTIN® Label to arrive at the claimed subject matter in Claims 1-8 for the reasons set forth in Ground 1 above (**Ex. 1016**, para. 18).

There would have been a reasonable expectation of success for doing so at least for the reasons set forth in Ground 1 above and further in view of the *in vivo* efficacy data of a similar immunoconjugate provided by Rosenblum 1999 (**Ex. 1018**, Figs. 12 and 13; **Ex. 1016**, para. 18).

C. Ground 3: Claims 1-8 Are Obvious Over Chari 1992 In View Of HERCEPTIN® Label, Further In View Of Hudziak 1998 And/Or Rosenblum 1999 And Further In View Of Baselga 1998 And/Or Pegram 1999

Chari 1992, HERCEPTIN® Label, Hudziak 1998 and Rosenblum 1999, have been described above. As described in **Table 1** above, Chari 1992 and HERCEPTIN® Label teach or suggest in combination each and every limitation recited in Claims 1-8. Baselga 1998 (**Ex. 1019**) and Pegram 1999 (**Ex. 1020**) provide further motivation and expectation of success for modifying Chari 1992's TA.1-maytansinoid conjugate into a HERCEPTIN®-maytansinoid conjugate as suggested by the combined teachings above (**Ex. 1016**, para. 19-21).

In particular, Baselga 1998 discloses a method to optimize the clinical role of HERCEPTIN® antibodies by administering them in combination with the antimicrotubule chemotherapeutic agent, paclitaxel. An enhanced, concentration-dependent inhibition of growth in cultures of ErbB2 overexpressing human

cancer cell lines treated with HERCEPTIN® plus paclitaxel was observed, as well as striking antitumor effects in breast carcinoma xenografts, resulting in the cure of well-established tumors (**Ex. 1019**, p. 2825, right col., 2nd para).

Baselga 1998 teaches that HERCEPTIN® has a higher affinity for $p185^{HER2}$ (K_D=0.1 nm) than the murine MAb 4D5, and has a cytostatic growth inhibitory effect against breast cancer cells expressing ErbB2/HER2 receptor (**Ex 1019**, p. 2825, left col.). Baselga 1998 further teaches that:

> "[t]he simplest explanation for the observed interaction between paclitaxel and rhuMAb HER2 is that it is the result of the summation of effects of two anticancer drugs that act on different targets; rhuMAb HER2 acts on the HER2 receptor signaling pathway and paclitaxel acts on tubulin" (**Ex. 1019**, paragraph abridging pp. 2829-2830).

Pegram 1999 discloses *in vivo* studies addressing ways to optimize the use of HERCEPTIN® in combination with established cancer therapeutics, including antimicrotubule chemotherapeutic agents paclitaxel (TAX) and vinblastine (VBL)(**Ex. 1020**, p. 2241, right col.; p. 2242, right col.). Significantly superior anti-tumor efficacy of HERCEPTIN® in combination with TAX, VBL and a number of other chemotherapeutic agents was observed when compared to effects of HERCEPTIN® alone or each chemotherapeutic drug alone (**Ex. 1020**, p. 2248, paragraph abridging left and right cols.).

Pegram 1999 teaches that most of the HERCEPTIN®/drug combinations demonstrate additive interactions, suggesting that the majority of the observed antiproliferative effects are due to a mechanism of action involving each agent acting independently. In particular, Pegram 1999 notes that the mechanisms of action of many of the drugs demonstrating additivity do not involve direct DNA damage, but rather disruption of microtubule polymerization/depolymerization (taxanes and vinca alkaloids) (**Ex. 1020**, p. 2248, left col. 2nd para). Pegram 1999 specifically teaches that "[t]he synergistic interaction of rhuMab HER2 with alkylating agents....as well as the additive interaction with taxanes, ... in HER-2/neu-overexpressing breast cancer cells demonstrates that **these are rational combinations to test in human clinical trials**" (*emphasis added)* (**Ex. 1020**, Abstract).

Reason to Combine and Reasonable Expectation of Success

As detailed, Baselga 1998 and Pegram 1999 add further weight to the motivation and expectation of success for modifying Chari 1992's TA.1-maytansinoid conjugate into a HERCEPTIN®-maytansinoid conjugate as suggested by the combined teachings of Chari 1992 and HERCEPTIN® Label, because both Baselga and Pegram suggest that HERCEPTIN® and maytansinoid may act independently and have an additive effort in inhibiting the growth of breast tumor cells (**Ex. 1016**, para. 21).

D. Ground 4: Claims 4 and 6-8 Are Obvious Based On Chari 1992 In View Of HERCEPTIN® Label And Further In View Of Morgan

As described in Ground 1 above, Chari 1992 and HERCEPTIN® Label teach or suggest in combination each and every limitation recited in Claims 4 and 6-8 of the '856 patent. Morgan 1990 (**Ex. 1021**) provides further motivation and expectation of success for using the succinimidyl 4-(N-maleimidomethyl)-cyclohexaqne-1-carboxylate (SMCC) linker in the huMAB4D5-8-maytansinoid conjugate suggested by the combined teachings of HERCEPTIN® Label and Chari 1992 (**Ex. 1016**, para. 22-24).

Morgan 1990 compares linkage properties in immunoconjugates comprising disulfide or thioether bonds linking a monoclonal antibody to a Pseudomonas toxin. Morgan 1990 teaches:

> The efficiency and kinetics of thioether formation were much higher with SMCC than with other maleimide reagents as well as more efficient than disulfide linkers. Thioether linkage resulted in immunotoxin consistently more potent and more selective *in vitro* than disulfide bonded conjugate. Thioether bonded conjugates also proved to have other favorable *in vivo* properties compared to disulfide conjugates: (1) a longer half-life in serum; (2) increased tumor localization; and (3) reduced toxicity. (**Ex. 1021**, Abstract)

In particular, Morgan 1990 teaches that higher doses of the thioether conjugates could be safely administered to primates, while providing a markedly improved yield, thereby improving the eventual efficiency and cost effectiveness of therapy with these agents (**Ex. 1021**, page 274, left col.). Morgan 1990 noted, "[w]hen tested for toxicity in both mice and monkeys, thioether conjugates were consistently 2-10 fold less toxic than comparable disulfide conjugates" (**Ex. 1021,** page 280, right col.). Morgan 1990 further teaches that "[t]he evidence from both long term (3 days or more) *in vitro* assays and animal toxicology experiments suggests that significant disruption of disulfide bonds can occur, leading to the release of PE that appears to be more toxic in free than conjugated form" and that "thioether bonded conjugates had a significantly longer serum half-life than disulfide conjugates, additional evidence for disulfide bond reduction *in vivo*" (**Ex. 1021**, page 281, left col.).

Reason to Combine and Reasonable Expectation of Success

As detailed in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 23-24), in view of the combined teachings Chari 1992, HERCEPTIN® Label and Morgan 1990, it would have been particularly obvious for an ordinarily skilled artisan to select Chari's thioether-bonded immunoconjugate (TA.1(noncleavable linker-May)$_4$) for substitution with the HERCEPTIN® antibody in HERCEPTIN® Label because HERCEPTIN®

antibody will reduce the immunogenicity of the immunoconjugate and the noncleavable SMCC linker would provide more favorable *in vivo* properties, such as longer half-life, increased tumor localization and reduced toxicity, compared to disulfide conjugates (**Ex. 1021**, Abstract).

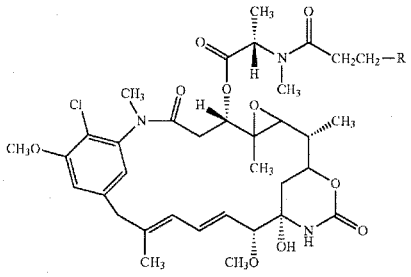
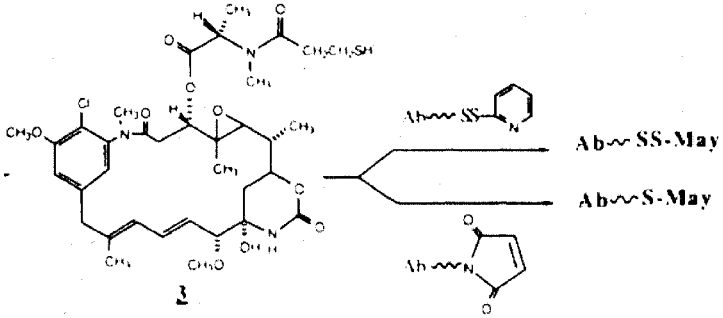
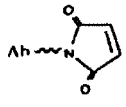
Although Chari 1992 notes that the TA.1(noncleavable linker-May) conjugate was less potent than the TA.1(cleavable linker-May) conjugate in an *in vitro* cytotoxicity assay (**Ex. 1012**, page 129, left col.), it is unclear whether this difference is also present in an *in vivo* setting. Further, even if conjugates containing noncleavable linkers are less potent *in vivo* than those containing cleavable linkers, the decreased potency may be compensated by the favorable *in vivo* properties of the non-cleavable linker described in Morgan 1990. Further, in view of the highly potent nature of maytansinoids (*i.e.,* 100- to 1000-fold higher cytotoxicity) (**Ex, 1012**, abstract), one would have nevertheless expected a reasonable expectation of success with respect to potency and toxicity.

E. Ground 5: Claims 1-4 and 6-8 Are Obvious Based On Chari 1992 In View Of Carter 1992

Chari 1992 (**Ex. 1012**) was published in January, 1992, more than a year before the earliest effective filing date of the '856 patent. Carter 1992 (**Ex. 1022**) was published in May, 1992, more than a year before the earliest effective filing date of the '856 patent. As detailed in **Table 2** below, the combination of Carter 1992 and Chari 1992 teaches or suggests each and every limitation recited in Claims 1-4 and 6-8.

Table 2

Claims	**Disclosure of Chari 1992 and Carter 1992**
1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8.	"We therefore prepared antibody conjugates of the maytansinoid 3 and the murine monoclonal antibody TA.1 (Fig. 2), using linkers containing either a disulfide bond or a noncleavable thioether bond. The TA.1 antibody binds to the HER-2/neu oncogene protein (also known as c-erb-2) that is expressed at high levels on human breast tumor cells (17)." (**Ex. 1012**, abridging paragraph between p. 128 and p.129) "One of seven additional humanized variants designed by molecular modeling (humAb4D5-8) binds the $p185^{HER2}$ antigen .... In addition, humAb4D5-8 has potency comparable to the murine antibody in blocking SK-BR-3 cell proliferation." (**Ex. 1022**, Abstract)

2. The immunoconjugate of claim 1, wherein the maytansinoid is DM1 having the structure:  and wherein the antibody is chemically linked to the maytansinoid via a disulfide or thioether group at "R" shown in the structure.	"We therefore prepared antibody conjugates of the maytansinoid 3 and the murine monoclonal antibody TA.1 (Fig. 2), using linkers containing either a **disulfide bond** or a noncleavable **thioether bond**" (**Ex. 1012**, p. 129, left col.)  Fig. 2 of Chari 1992 (see above) shows maytansinoids and their conjugation to antibodies (**Ex. 1012**, p. 128, right col.). Compound 3 is DM1, which reacts with linker modified antibody (or ) via the -SH group (which corresponds to the "R" group in Claim 2) to form the immunoconjugate Ab~SS-May or Ab~S-May (Fig. 2).
3. The immunoconjugate of claim 1, wherein the immunoconjugate comprises from 3 to 5 maytansinoid molecules per antibody molecule.	Chari 1992 teaches the TA.1(-SS-May)$_n$ conjugates, where n is an average number of maytansinoid molecules per antibody and where n can be 4 (**Ex. 1012**, p. 129, Table 2)
4. The immunoconjugate of claim 1, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from **N-succinimidyl-3-(2-pyridyldithio) propionate,** N-	"In order to generate antibody-drug conjugates the antibody was modified with **SPDP [*N*-succinimidyl-3-(2-pyridyldithio)-propionate]** to introduce dithio-pyridyl groups, **or** with **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2 was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies."

succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and **succinimidyl-4-(N-maleimidomethyl)cyclohexanel-1-carboxylate**.	(**Ex. 1012**, p. 128, bottom right col. Legend of Fig. 2)
6. The immunoconjugate of claim 4, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"In order to generate antibody-drug conjugates the antibody was modified … with **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2 was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies" (**Ex. 1012**, p. 128, Legend of Fig.2)
7. The immunoconjugate of claim 2, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from N-succinimidyl-3-(2-pyridyldithio)propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"In order to generate antibody-drug conjugates the antibody was modified with **SPDP [*N*-succinimidyl-3-(2-pyridyldithio)-propionate]** to introduce dithio-pyridyl groups, or with **SMCC [succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2 was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies" (**Ex. 1012**, p. 128, Legend of Fig.2)
8. The immunoconjugate of claim 7, wherein the antibody and the	"In order to generate antibody-drug conjugates the antibody was modified with … **SMCC [succinimidyl-4-(*N*-**

maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	**maleimidomethyl)cyclohexane-1-carboxylate]** to introduce maleimido groups. May-SS-Me 2was reduced to May-SH 3 (see "Materials and Methods") and reacted with the modified antibodies." (**Ex. 1012**, p. 128, Legend of Fig. 2)

Intended use of a composition does not render the composition nonobvious

Claims 1-4 and 6-8 are directed to an immunoconjugate comprising huMAb4D5-8 conjugated to a maytansinoid. It is well established in patent law that intended use of a composition does not, in and of itself, render the composition nonobvious (see *e.g.*, *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) "Products of identical chemical composition cannot have mutually exclusive properties," and *In re Zierden*, 411 F.2d 1325, 1328 (CCPA 1969) "A mere statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable").

Chari 1992 and Carter 1992 teach every and each limitation of Claims 1-4 and 6-8 of the '856 patent

As shown in **Table 2** above, Chari 1992 discloses an immunoconjugate comprising a maytansinoid chemically linked to a mouse anti-ErbB2-antibody (**Ex. 1012**, Fig. 2). Chari 1992 also discloses that the maytansinoid is DM1 and that the antibody is chemically linked to the maytansinoid *via* a disulfide or thioether group at "R" position (**Ex. 1012**, Fig. 2), as recited in Claim 2 of the

'856 patent. The immunoconjugate of Chari 1992 may comprise from 3-5 maytansinoid molecules per antibody molecule (**Ex. 1012**, p. 129, bottom right col. Table 2), as recited in Claim 3 of the '856 patent. The antibody and the maytansinoid were conjugated by a chemical linker selected from SPDP or SMCC (**Ex. 1012**, p. 128, bottom right col., Fig. 2), as recited in Claims 4 and 6-8 of the '856 patent.

Chari 1992 does not explicitly disclose huMAB4D5-8. However, Carter 1992 discloses the humanization of mouse monoclonal antibody mumAb4D5 and humanized mumAb4D5 variant huMAB4D5-8 (**Ex. 1022**, Abstract). Carter 1992 teaches that the efficacy of mumAb4D5 in human cancer therapy is likely to be limited by a human anti-mouse antibody response and lack of effector functions (**Ex. 1022**, Abstract). Carter 1992 further teaches that huMAB4D5-8 much more efficient in supporting antibody-dependent cellular cytotoxicity against SK-BR-3 cells than mumAb4D5 (**Ex. 1022**, Abstract).

As confirmed by the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 25-26), based on the teachings of Chari 1992 and Carter 1992, it would be obvious to an ordinarily skilled artisan, at the time the '856 patent was filed, to substitute the mouse mAb TA.1 in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8 of Carter 1992.

Reason to Combine and Reasonable Expectation of Success

An ordinarily skilled artisan would be motivated to substitute the mouse mAb TA.1 in the immunoconjugate of Chari 1992 with the humanized mAb huMAB4D5-8 because the efficacy of mouse mAb TA.1 in human cancer therapy is likely to be limited by a human anti-mouse antibody response and lack of effector functions and because huMAB4D5-8 has been shown to be effective in supporting antibody-dependent cellular cytotoxicity against SK-BR-3 cells (**Ex. 1022**, Abstract).

As discussed above in Ground 1, an ordinarily skilled artisan would have had a reasonable expectation of success because substituting a mouse anti-ErbB2 antibody in an immunoconjugate with a humanized anti-ErbB2 antibody is no more than a simple substitution of one known element for another to obtain a predictable result (**Ex. 1016**, para. 14). Further, based on the detailed description in Chari 1992 and the general knowledge in the art about conjugation of maytansinoids with antibodies, an ordinarily skilled artisan would have known how to substitute the mouse mAb TA.1 in the immunoconjugate of Chari 1992 with huMAB4D5-8 to produce an immunoconjugate of maytansinoid and huMAB4D5-8. As confirmed by the Declaration of Dr. Rosenblum, maytansinoid-huMAB4D5-8 conjugate can be produced using the conjugation process described in Chari 1992 (**Ex. 1016**, para. 14).

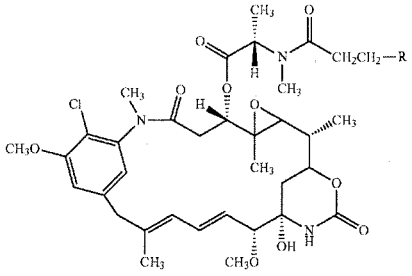
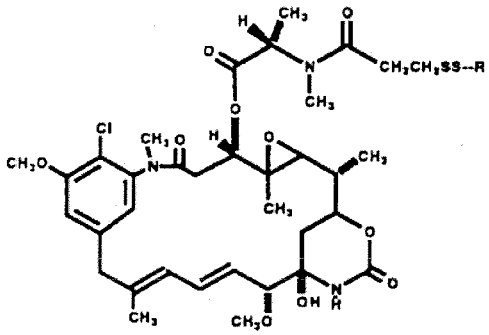
As noted in MPEP, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination (MPEP 2144(II)).

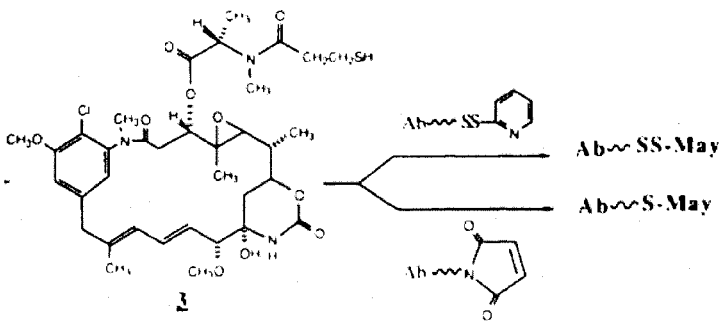
In the instant case, there was clearly a recognition that some advantage or expected beneficial result (*e.g.*, avoiding immune response to mouse antibody and improving effector functions) would have been produced by the combination of Chari 1992 and Carter 1992, based on established scientific principles at the time of the priority date of the '856 patent.

F. Ground 6: Claims 1-5 and 7 Are Obvious Over Liu 1996 In View Of HERCEPTIN® Label

Liu, *et al.*, 1996 (*Proc. Natl. Acad. Sci. USA*, 93:8618-8623 (1996) (Liu 1996), **Ex. 1023**) was published in August, 1996, more than a year before the earliest effective filing date of the '856 patent. HERCEPTIN® Label (**Ex. 1008**) was published in September 1998, more than a year before the earliest effective filing date of the '856 patent. As detailed in **Table 3** below, the combination of Liu 1996 and HERCEPTIN® Label teaches or suggests each and every limitation recited in Claims 1-5 and 7.

Table 3

Claims	Disclosure of Liu 1996, HERCEPTIN® Label and Morgan 1990
1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8.	"The immunoconjugate C242-DM1 was prepared by conjugating DM1 to the monoclonal antibody C242" (**Ex. 1023**, Abstract) **"HERCEPTIN® (Trastuzumab)** is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd=5nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2" (**Ex. 1008**, p. 1, top left col.)
2. The immunoconjugate of claim 1, wherein the maytansinoid is DM1 having the structure:  and wherein the antibody is chemically linked to the maytansinoid via a disulfide or thioether	"C242-DM1 (compound 3) was prepared as described (12)" (**Ex. 1023**, p8618, right col. 3rd para).  **2 DM1: R = Me** **3 C242-DM1: R = C242** As shown in compound 3, the antibody (C242) is chemically linked to the maytansinoid (DM1) via a disulfide group (SS) at "R" shown in the structure of Claim 2.

group at "R" shown in the structure.	Note: Reference 12 of Liu 1996 is Chari 1992 (**Ex. 1012**) which provides  3
3. The immunoconjugate of claim 1, wherein the immunoconjugate comprises from 3 to 5 maytansinoid molecules per antibody molecule.	"The conjugate contains, on the average, four covalently linked DM1 molecules per antibody molecule" (**Ex. 1023**, p. 8619, right col. 4th para).
4. The immunoconjugate of claim 1, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from N-succinimidyl-3-(2-pyridyldithio) propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and succinimidyl-4-(N-maleimidomethyl)cyclohexanel-1-carboxylate.	"Ansamitocin P-3 (compound 1) provided by Takeda (Osaka) was converted to the disulfide-containing maytansinoid DM1 (compound 2) (Fig. 1) as described (15)" (**Ex. 1023**, p. 8618, right col. 3rd para). Note: Reference 15 of Liu 1996 is US 5,208,020 (**Ex. 1024**) which provides (at col. 1, lines 28-30, and col. 21, lines 15-25) a disulfide-containing maytansinoid-antibody conjugate with **SPDP [*N*-succinimidyl-3-(2-pyridyldithio)-propionate]** chemical linker.

5. A pharmaceutical composition comprising an immunoconjugate of any of claims 1 to 4, and a pharmaceutically acceptable carrier.	"Each vial of HERCEPTIN® contains 440mg Trastuzumab, 9.9mg L-histidine HCl, 6.4mg L-histidine, 400mg α,α-trehalose dehydrate, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection, (BWFI) USP" (**Ex. 1008**, p. 1, top left col.)
6. The immunoconjugate of claim 4, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"Conjugates of monoclonal antibodies and Pseudomonas exotoxin A (PE) were formed with disulfide or thioether bonds. Thioether conjugates which formed with succinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (SMCC) modified PE and reduced antibody formed with an 80% yield of equimolar conjugate within 30 min…" (Morgan 1990, **Ex. 1021**, Abstract)
7. The immunoconjugate of claim 2, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from N-succinimidyl-3-(2-pyridyldithio)propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"Ansamitocin P-3 (compound 1) provided by Takeda (Osaka) was converted to the disulfide-containing maytansinoid DM1 (compound 2) (Fig. 1) as described (15)." (**Ex. 1023**, p8618, right col. 3rd para). Note: Reference 15 of Liu 1996 is US 5,208,020 (**Ex. 1024**) which provides (at col. 1, lines 28-30, and col. 21, lines 15-25) a disulfide-containing maytansinoid-antibody conjugate with **SPDP [*N*-succinimidyl-3-(2-pyridyldithio)-propionate]** chemical linker.
8. The immunoconjugate of claim 7, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"Conjugates of monoclonal antibodies and Pseudomonas exotoxin A (PE) were formed with disulfide or thioether bonds. Thioether conjugates which formed with succinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (SMCC) modified PE and reduced antibody formed with an 80% yield of equimolar conjugate within 30 min…" (Morgan 1990, **Ex. 1021**, Abstract)

Intended use of a composition does not render the composition nonobvious

Claims 1-5 and 7 are directed to an immunoconjugate comprising huMAb4D5-8 conjugated to a maytansinoid. It is well established in patent law that intended use of a composition does not, in and of itself, render the composition nonobvious (see *e.g.*, *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) "Products of identical chemical composition cannot have mutually exclusive properties," and *In re Zierden*, 411 F.2d 1325 (CCPA 1969) "A mere statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable").

Liu 1996 and HERCEPTIN® Label disclose each and every limitation of Claims 1-5 and 7 of the '856 patent

As shown above, Liu 1996 discloses an immunoconjugate comprising a maytansinoid chemically linked to an antibody (**Ex. 1023**, Fig. 1), as recited in Claim 1 of the '856 patent. Liu 1996 further discloses that the maytansinoid is DM1 and that the antibody is chemically linked to the maytansinoid *via* a disulfide at "R" position, as recited in Claim 2 of the '856 patent, that the immunoconjugate comprises 4 maytansinoid molecules per antibody molecule, as recited in Claim 3 of the '856 patent, and that the antibody and the maytansinoid are conjugated by a chemical linker selected from SPDP, as recited in Claims 4 and 7 of the '856 patent.

Liu 1996 does not explicitly disclose huMAB4D5-8 (recited in Claim 1 of the '856 patent) or a pharmaceutically acceptable carrier (recited in Claim 5 of the '856 patent). However, HERCEPTIN® Label describes the clinical use of huMAB4D5-8 (*i.e.*, HERCEPTIN®), which is described as being indicated for the treatment of patients with metastatic breast cancer. HERCEPTIN® Label also describes the injection of HERCEPTIN® with a pharmaceutically acceptable carrier (Bacteriostatic Water for Injection, **Ex. 1008**, p. 1, top left col.).

As confirmed by the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 27-28), it would be obvious to an ordinarily skilled artisan, at the time of the priority date of the '856 patent, to substitute the C242 antibody (which binds to the CanAg of colon cancer cells) in the immunoconjugate of Liu 1996 with the humanized mAb huMAB4D5-8 for the treatment of breast cancer, and to produce a pharmaceutical composition comprising the maytansinoid-huMAB4D5-8 conjugate and a pharmaceutically acceptable carrier based on the teachings of Liu 1996 and HERCEPTIN® Label, as well as the general knowledge in the art at that time. Further, a combination of known elements would have been *prima facie* obvious if an ordinarily skilled artisan would have recognized an apparent reason to combine those elements and would have known how to do so. *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1350 (Fed. Cir. 2009).

Reason to Combine and Reasonable Expectation of Success

As described in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 29), an ordinarily skilled artisan would be motivated to substitute the C242 antibody in the immunoconjugate of Liu 1996 with the humanized mAb huMAB4D5-8 for the treatment of breast cancer, because:

(1) the immunoconjugate of Liu 1996 is shown to be highly cytotoxic towards cultured cancer cells in an antigen-specific manner and showed remarkable anti-tumor efficacy *in vivo* (**Ex. 1023**, Abstract);

(2) huMAB4D5-8 selectively binds to ErbB2 with high affinity and has been approved for use in humans (**Ex. 1008,** p. 1, left col.); and

(3) clinical studies indicated that huMAB4D5-8 works well in combination with microtubule-directed chemotherapy agents for the treatment of breast cancer (**Ex. 1008**, p. 1, left col.).

Based on the description in Liu 1996 and the general knowledge in the art about conjugation of maytansinoids with antibodies, an ordinarily skilled artisan would have known how to substitute the C242 antibody in the immunoconjugate of Liu 1996 with huMAB4D5-8 to produce an immunoconjugate of maytansinoid and huMAB4D5-8. The conjugation process described in Liu 1996 for producing C242-DM1 conjugates would be equally applicable to the production of huMAB4D5-8-DM1 conjugate (**Ex. 1023**).

In addition, there would have been a reasonable expectation of success for an immunoconjugate comprising huMAB4D5-8 conjugated to a microtubule-targeting drug, such as maytansinoid because huMAB4D5-8 is more effective in treating breast cancer when used in combination with the microtubule targeting drug, paclitaxel (**Ex. 1008**) and maytansinoid is also a microtubule targeting drug that was known in the art to be more potent than paclitaxel (as supported by **Ex. 1012,** Abstract). Further, huMAB4D5-8 selectively binds to ErbB2 with high affinity and has been approved for use in humans (**Ex. 1008,** p. 1, left col.). In addition, an immunoconjugate containing a "humanized" antibody would be less immunogenic in humans.

G. Ground 7: Claims 6 and 8 Are Obvious Over Liu 1996 In View Of HERCEPTIN® Label And Further In View of Morgan 1990

Liu 1996 and HERCEPTIN® Label teach a HERCEPTIN®-DM1 conjugate but do not disclose "wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate," as recited in Claims 6 and 8.

Morgan 1990, as noted in **Table 3** above, teaches that higher doses of immunoconjugates containing non-cleavable **succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate** linker could be safely administered to primates, while providing a markedly improved yield,

thereby improving the eventual efficiency and cost effectiveness of therapy with these agents (**Ex. 1021**, page 274, left col.). Morgan 1990 noted, "[w]hen tested for toxicity in both mice and monkeys, thioether conjugates were consistently 2-10 fold less toxic than comparable disulfide conjugates" (**Ex. 1021**, page 280, right col.). Morgan 1990 further teaches that "[t]he evidence from both long term (3 days or more) *in vitro* assays and animal toxicology experiments suggests that significant disruption of disulfide bonds can occur, leading to the release of PE that appears to be more toxic in free than conjugated form" and that "thioether bonded conjugates had a significantly longer serum half-life than disulfide conjugates, additional evidence for disulfide bond reduction *in vivo*" (**Ex. 1021**, page 281, left col.).

Reason to Combine and Reasonable Expectation of Success

In view of the combined teachings of Liu 1996, HERCEPTIN® Label and Morgan 1990, it would have been obvious for an ordinarily skilled artisan to prepare a HERCEPTIN®-maytansinoid immunoconjugate with a SMCC linker for the treatment of breast cancer, because HERCEPTIN® antibody will reduce the immunogenicity of the immunoconjugate and the noncleavable SMCC linker would provide more favorable *in vivo* properties, such as longer half-life, increased tumor

localization and reduced toxicity, compared to disulfide conjugates (**Ex. 1021**, Abstract; **Ex. 1016**, para. 30).

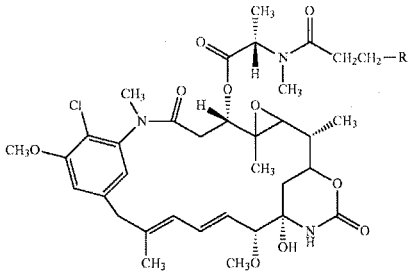
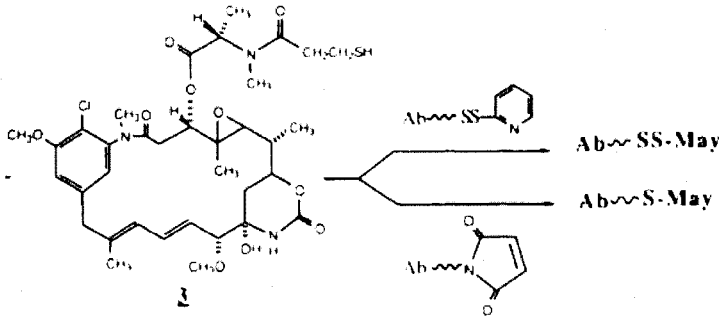
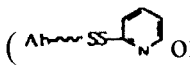
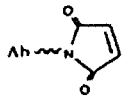
H. Ground 8: Claims 1-8 Are Obvious Over Cohen 1999 In View Of Chari 1992

Cohen (U.S. Patent Application Publication No. 2003/0170235; **Ex. 1025**) was published on September 11, 2003 with a priority date of May 14. 1999 (accordingly, "Cohen 1999"). Cohen 1999 does not share any of the named inventors in the '856 patent, nor is Cohen 1999's invention commonly assigned with the '856 patent. Therefore, Cohen 1999 is by "another" and qualifies as prior art under 35 U.S.C. §102(e)/103(a).

As detailed in **Table 4** below, the combination of Cohen 1999 and Chari 1992 teaches or suggests each and every limitation recited in Claims 1-8.

Table 4

Claims	**Disclosure of Cohen 1999 and Chari 1992**
1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid,	"Conjugates of an antibody and one or more small molecule toxins, such as a calicheamicin, a maytansine (U.S. Pat. No. 5,208,020), a trichothene, and CC1065 are also contemplated herein. In one preferred embodiment of the invention, the antibody is conjugated to one or more maytansine molecules (e.g. about 1 to about 10 maytansine molecules per antibody molecule). Maytansine may, for example, be converted to May-SS-Me which may be reduced to May-SH3 and reacted with modified antibody (Chari *et al.* Cancer Research 52: 127-131 [1992]) to generate a maytansinoid-antibody

	immunoconjugate" (**Ex. 1025**, para [0113])
wherein the antibody is huMAb4D5-8.	"A humanized version of the murine 4D5 antibody (HERCEPTIN®) was engineered by inserting the complementarity determining regions of the murine 4D5 antibody into the framework of a consensus human immunoglobulin (IgG1)" (**Ex. 1025**, para [0155])
2. The immunoconjugate of claim 1, wherein the maytansinoid is DM1 having the structure:  and wherein the antibody is chemically linked to the maytansinoid via a disulfide or thioether group at "R" shown in the structure.	"We therefore prepared antibody conjugates of the maytansinoid 3 and the murine monoclonal antibody TA.1 (Fig. 2), using linkers containing either a **disulfide bond** or a noncleavable **thioether bond**" (**Ex. 1012**, p. 129, left col.)  Fig. 2 of Chari 1992 (see above) shows maytansinoids and their conjugation to antibodies (**Ex. 1012**, p. 128, right col.). Compound 3 is DM1, which reacts with linker modified antibody ( or ) via the -SH group (which corresponds to the "R" group in Claim 2) to form the immunoconjugate Ab~SS-May or Ab~S-May (Fig. 2).
3. The immunoconjugate of claim 1, wherein the immunoconjugate comprises from 3 to 5 maytansinoid molecules per antibody molecule.	"In one preferred embodiment of the invention, the antibody is conjugated to one or more maytansine molecules (e.g. about 1 to about 10 maytansine molecules per antibody molecule)" (**Ex. 1025**, para [0113])

4. The immunoconjugate of claim 1, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from N-succinimidyl-3-(2-pyridyldithio) propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and succinimidyl-4-(N-maleimidomethyl)cyclohexanel-1-carboxylate.	"Conjugates of the antibody and cytotoxic agent maybe made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate…" (**Ex. 1025**, para [0118])
5. A pharmaceutical composition comprising an immunoconjugate of any of claims 1 to 4, and a pharmaceutically acceptable carrier.	"Therapeutic formulations of the antibodies used in accordance with the present invention are prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions" (**Ex. 1025**, para [0135])
6. The immunoconjugate of claim 4, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"Conjugates of the antibody and cytotoxic agent maybe made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate…" (**Ex. 1025**, para [0118])
7. The immunoconjugate of claim 2, wherein the antibody and the maytansinoid are conjugated by a chemical linker selected from N-succinimidyl-3-(2-	"Conjugates of the antibody and cytotoxic agent maybe made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate…" (**Ex. 1025**, para [0118])

pyridyldithio)propionate, N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) and succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	
8. The immunoconjugate of claim 7, wherein the antibody and the maytansinoid are conjugated by succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.	"Conjugates of the antibody and cytotoxic agent maybe made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate..." (**Ex. 1025**, para [0118])

Cohen 1999 and Chari 1992 teach or suggest in combination each and every limitation recited in Claims 1-8. In particular, Cohen 1999 teaches immunoconjugates comprising a maytansinoid chemically linked to an antibody (**Ex. 1025**, para [0113]) and humanized versions of the murine anti-ErbB2 antibody 4D5 (huMab4D5-8) (**Ex. 1025**, para [0155]), as recited in Claim 1 of the '856 patent. Cohen 1999 further teaches immunoconjugates comprising from 3-5 maytansinoid molecules per antibody molecule (**Ex. 1025**, para [0113]), as recited in Claim 3 of the '856 patent, and immunoconjugates with a chemical linker such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP) or succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (**Ex. 1025**, para [0118]), as recited in Claims 4 and 6-8 of the '856 patent. Cohen 1999 also teaches a

pharmaceutically acceptable carrier (**Ex. 1025**, para [0135]), as recited in Claim 5 of the '856 patent. Cohen 1999 does not teach conjugation to the specific maytansinoid, DM1 at the "R" position. This deficiency is made up by Chari 1992 (**Ex. 1012**, Fig. 2).

As discussed in more detail in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 31-32), it would have been prima facie obvious to an ordinarily skilled artisan, at the time of the priority date of the '856 patent, to make the anti-ErbB2 humanized antibody-maytansinoid conjugate taught by Cohen 1999 using the DM1 maytansinoid taught by Chari 1992. An ordinarily skilled artisan would have been motivated to do so with a reasonable expectation of success based on the teachings of Cohen 1999 and Chari 1992, because Cohen 1999 teaches an anti-ErbB2 humanized antibody (huMab4D5-8) with high affinity for ErbB2, and Chari 1992 teaches an anti-ErbB2 antibody-DM1 conjugate with high antigen-specific cytotoxicity in vitro, low systemic toxicity *in vivo* and favorable pharmacokinetic behavior. It would have been obvious to substitute the mouse anti-ErbB2 antibody in Chari's antibody-DM1 immunoconjugate with the anti-ErbB2 humanized antibody (huMab4D5-8) of Cohen 1999 for increased tumor targeting and decreased immunogenicity of the conjugate. Further, in view of the highly potent nature of DM1 as described in Chari 1992 ("100- to 1000-fold

higher cytotoxicity"), one would have nevertheless expected a reasonable expectation of success with respect to potency and toxicity.

Cohen 1999 qualifies as a prior art reference under 35 USC 103(a)

During the prosecution of the '856 patent, a Declaration under 37 C.F.R. §1.132 by co-inventors Blättler and Chari was submitted, stating that the subject matter claimed in the '856 patent, which is disclosed but not claimed in a number of references listed in Appendix A (which includes Cohen 1999), is their own work, and not the invention "of another" **(Ex. 1026)**.

Petitioner requests the Board's consideration of the legal grounds for filing such declarations to overcome a prospective invalidity contention concerning Cohen 1999. Applicants' statement in **Ex. 1026** that "a 35 U.S.C. 102(e) rejection can be overcome by...submitting an affidavit or declaration under 37 C.F.R. 1.132 establishing that the relevant disclosure is applicant's own work" is described in MPEP 2136.05 with reference to *In re Mathews*, 408 F.2d 1393, 161 USPQ 276 (CCPA 1969). However, again referencing *In re Mathews*, MPEP 2136.05 further states that "[s]uch a showing can be made by proving that the patentee, or **the inventor(s) of the U.S. patent application publication or the international application publication, was associated with applicant (*e.g.* worked for the same company) and learned of applicant's invention from applicant." Further, MPEP provides that

> A showing that the reference disclosure arose from applicant's work **coupled with a showing of conception by the applicant before the filing date of the reference** will overcome the 35 U.S.C. 102(e) rejection (MPEP 2136.05). *In re DeBaun*, 687 F.2d 459, 214 USPQ 933 (CCPA 1982) (Declaration submitted by DeBaun stated that he was the inventor of subject matter disclosed in the U.S. patent reference of DeBaun and Noll. Exhibits were attached to the declaration showing conception and included drawings DeBaun had prepared and given to counsel for purposes of preparing the application which issued as the reference patent. The court held that, even though the evidence was not sufficient to antedate the prior art patent under 37 C.F.R 1.131, diligence and/or reduction to practice was not required to show DeBaun invented the subject matter. Declarant's statement that he conceived the invention) (MPEP 2136.05, *emphasis added*).

The Declaration of Blättler and Chari, however, does not mention anything about the association between the inventors of the references listed in Appendix A of their declaration (**Ex. 1026**) and the inventors of the '856 patent, as required per *In re Mathews*. Nor does the Declaration provide any showing of conception by the applicant before the filing date of the reference, as required by *In re DeBaun*. Accordingly, Petitioner respectfully submits that the Declaration of Blättler and Chari fails to provide sufficient legal grounds to overcome a prospective invalidity contention based on the references listed in Appendix A.

VII. ISSUES RAISED DURING PROSECUTION OF THE '856 PATENT

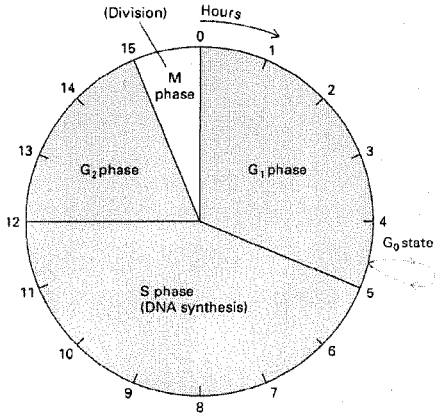
A. Patentee Argued the Existence of an Incompatible Mechanism of Action Between HERCEPTIN® and Maytansinoid

During prosecution of the '856 patent, Patentee argued that an ordinarily skilled artisan would not have been motivated to conjugate huMAb4D5-8 with a maytansinoid because the respective mechanisms of action of MAbD5 and maytansinoids would have counseled against making such a conjugate (July 6, 2010 Response to Office Action of June 8, 2010, p. 7, **Ex. 1027**). Patentee supported the argument with a Declaration by Mark X. Sliwkowski, Ph.D. (the "Sliwkowski Declaration," **Ex. 1028**) which states: (1) "that sensitivity of cells to the cytotoxic effect of maytansine was cell cycle-dependent, *with cells synchronized in G1 being the most resistant to maytansine*" (emphasis in original) and with cells in M-phase being most sensitive to maytansine and (*Id.* at para. 10); and, (2) that huMAb4D5-8 acts at least in part by arresting breast cancer cells in the G_0/G_1 phase of the cell cycle (*Id.* at para 11), which precedes the subsequent S, G_2 and M (mitosis) phase of the cell cycle. Based on the above statements, Dr. Sliwkowski concluded that an ordinarily skilled artisan would not have been motivated to select huMAb4D5-8 as a humanized anti-HER2 antibody for conjugation to a maytansinoid, such as DM1, since "it would have expected that huMAb4D5-8

would arrest cancer cells in the pre-mitotic G_0/G_1 phase of the cell cycle before DM1 would even have the opportunity to act" (*Id.* at para 12). Nevertheless, it had been well established, at the time of the priority date of the '856 patent, that huMAb4D5-8 exhibits an anti-tumor additive effective with microtubule-directed chemotherapy agents (see **Ex. 1016**, para. 33-34). As discussed above, Baselga 1998 describes that HERCEPTIN® **enhances** the antitumor activity of paclitaxel and doxorubicin against HER2/neu-overexpressing human breast cancer xenografts (**Ex. 1019**, Abstract). Pegram 1999 also demonstrates **additive** interaction of HERCEPTIN® with taxanes in HER2/neu-overexpressing breast cancer cells. Pegram 1999 specifically teaches that "[t]he synergistic interaction of rhuMab HER2 with alkylating agents....as well as the additive interaction with taxanes, ... in HER-2/neu-overexpressing breast cancer cells demonstrates that these are rational combinations to test in human clinical trials" (**Ex. 1020**, Abstract). In addition, a clinical study described in Table 1 of the HERCEPTIN® Label showed synergistic or additive effect between HERCEPTIN® and the antimicrotubule chemotherapy agent paclitaxel (**Ex. 1008**, page 1, left col.; **Ex. 1016**, para.34).

Moreover, as shown in Figure 1 below and described in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 35), a cell cycle constitutes multiple phases (*i.e.*, G_0/G_1, S, G_2 and M phases). At any given time, many of the breast cancer cells in

a patient would not be in the G_0/G_1 phase. It was not clear, at the time of the priority date of the '856 patent, that when HERCEPTIN®-maytansinoid immunoconjugates bind to HER2-expressing breast cancer cells that are not in the G_0/G_1 phase, the conjugates will cause the G_0/G_1 arrest in these cells before the maytansinoid is internalized and/or released from the conjugates.



G1 - first gap

S - DNA synthesis (replication)

G2 - second gap

M - mitosis

Figure 1: Cell Cycle

In addition, even if the binding the HERCEPTIN®-maytansinoid conjugate to HER2 expressing breast cancer cells causes G_0/G_1 block in those cells, there was no evidence that the cells would indefinitely stay in the G_0/G_1 phase. If the cells are released from the G_0/G_1 block after the internalization of the conjugate, they would no longer be resistant to maytansinoid toxicity after maytansinoid is released from the conjugate (**Ex. 1016**, para. 36).

Finally, there was no evidence that internalized maytansinoid would not kill breast cancer cells in G_0/G_1 phase. Considering the facts that

(1) maytansinoid was known in the art to be 100- to 1000-fold more potent than clinically used anticancer drugs at that time (supported by **Ex. 1012**, abstract) and (2) the targeted delivery to HER2 overexpressing breast cancer cells would allow internalization of maytansinoid at a much higher concentration than that would be achievable without the conjugate, it is not unreasonable to expect effective killing of breast cancer cells in G_0/G_1 phase by the HERCEPTIN®-maytansinoid conjugate (**Ex. 1016**, para. 37).

Dr. Sliwkowski's statement that HERCEPTIN® is *cytostatic* (i.e., causing arrest of cycle but not cell death, **Ex. 1028**, para. 11) provides further motivation for combining HERCEPTIN® with a more potent cytotoxic agent such as maytansinoid. As detailed in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 38), the inventors of the '856 patent co-authored a post-filing publication with Dr. Sliwkowski (Phillips 2008) attesting to this fact:

> Because the effect of trastuzumab is cytostatic in nature, the enhanced potency of the ADC is, thus, due to exposure of the cells to the cytotoxic maytansinoid. (**Ex. 1004**, p. 9283, top left col.).

The above-cited publication admits that the underlying basis for the claims of the '856 patent was predicated on the results obtained before the priority date of the '856 patent:

> Because HER2 is highly differentially expressed on breast tumor cells (1-2 million copies per cell) compared with normal epithelial cells, HER2 represents an ideal target for antibody-drug conjugate (ADC) therapy. Numerous preclinical and clinical studies indicate that **trastuzumab combines extremely well with microtubule-directed agents (29-32)**. Given the mechanism of action and potency of maytansine, it was deemed to be a particularly attractive cytotoxic agent to conjugate to trastuzumab. (**Ex. 1004**, p. 9281, top left col., emphasis added).

The statements cited above clearly concede the obviousness to combine huMABD5-8 with maytansinoid in an immunoconjugate. All the facts described in the statements were known to an ordinarily skilled artisan at the time of the priority date of the '856 patent. Specifically, the statements demonstrate that recognition that trastuzumab "combines extremely well with microtubule-directed agents," was *not* something discovered after the time the alleged invention was made. To the contrary, the preclinical studies cited in **Ex. 1004** as reference 29 (Baselga 1998, **Ex. 1019**) and reference 30 (Pegram 1999, **Ex. 1020**) were published before the priority date of the '856 patent.

Further, in describing the inventors' approach to forming antibody-DM1 conjugates in accordance with the '856 patent, Phillips 2008 states that "[a]ntibody-DM1 conjugates were originally designed with a disulfide-based

linker for release of active drug by intracellular reduction (24)" (**Ex. 2004**, page 9282, bottom right col.). Since Reference 24 of **Ex. 2004** corresponds to Chari 1992 (**Ex. 1012**), this statement is a tacit admission by the inventors of the '856 patent, as well as by Dr. Sliwkowski, that the underlying basis for the '856 patent is to be found in Chari 1992.

B. Reasonable Expectation of Success

The Sliwkowski Declaration furthers a review article by Trail and Bianchi (Exhibit H of **Ex. 1028**) for the proposition that it would not have been obvious to conjugate a humanized anti-HER2 antibody to a maytansinoid, since it would have been unpredictable whether such a conjugate would effectively and safely treat a HER2 overexpressing cancer with a reasonable expectation of success. In this regard, the Sliwkowski Declaration relies on the Trail article as suggesting that, before the priority date, the utility of immunoconjugates was often limited due to the expression of the targeted antigen on normal as well as cancerous cells, making it necessary to balance the relative selectivity of the MAb for cancerous cells over normal cells (**Ex. 1028**, para 13 and 15). More particularly, the Sliwkowski Declaration highlights the Trail article cautioning that "[t]he use of extremely toxic drugs requires careful MAb [monoclonal antibody] selection *as even low levels of expression of the targeted antigen by normal cells may lead to*

significant toxicity" (**Ex. 1028**, para 13, emphasis in original). In view of these suggestions, the Sliwkowski Declaration states:

> Accordingly, even if huMAb4D5-8 had not negated the cytotoxicity of DMl (an outcome which would not have been expected), it would nonetheless have been unpredictable as to whether a huMAb4D5-8-DMl immunoconjugate would have achieved an appropriate balance between antibody selectivity (i.e., for cancerous cells versus normal cells) and potency of the cytotoxic agent. HER2 is expressed on normal cells as well as being overexpressed on certain breast cancer cells and other cancer cells. Therefore ... it would have been unpredictable whether such an immunoconjugate would have been unacceptably toxic due to delivery of DMl to normal cells expressing HER2. The present application addresses this unpredictability, reporting that *"HERCEPTIN®-DM1 does not kill normal human cells, indicating a selective* activity," based on studies in which "[t]he effect of various concentrations of HERCEPTIN®-DM1 on hummman [sic, human] mammary epithelial cells, human hepatocytes and human small airway epithelial cells was investigated...." (**Ex. 1028**, para 14)

As detailed in the Declaration of Dr. Rosenblum (**Ex. 1016**, para. 41-43), contrary to the statements above, before the priority date of the '856 patent, maytansinoid immunoconjugates were demonstrated to be substantially free of toxicity, based on the same kinds of assays described in the '856 patent. For

example, Chari 1992 describes an immunoconjugate comprising the maytansinoid, DM1 conjugated to an anti-ErbB2 antibody TA.1 (**Ex. 1012**). This conjugate demonstrated a strong and highly selective concentration-dependent cytotoxic effect on a human breast cancer cell line SK-BR-3 (99.9% killing of ErbB2 receptor-positive SK-BR-3 cells at 0.1 nm concentration and at least 1000-fold less cytotoxicity toward ErbB2 receptor-negative KB cells) (**Ex. 1012**, p 129, left col. 3rd para) and low systemic toxicity *in vivo* (**Ex. 1012,** Abstract). Chari 1992 further reported a pharmacological study in which mice were injected with a conjugate (A7(-SS-May)$_6$), which was found it to be "not toxic for the animals." This led Chari 1992 to conclude that "[t]he high specific cytotoxicity of maytansinoid conjugates toward tumor cell lines in conjunction with their low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (**Ex. 1012**, p. 130, left col.).

Such safety studies are not limited to the report in Chari 1992. Liu *et al.* (**Ex. 1023**) reported preclinical efficacy tests using the antibody-maytansinoid conjugate, C242-DM1 in a human colorectal cancer model. C242-DM1 was found to be 1100-fold less cytotoxic for antigen-negative A-375 control cells and when administered by *i.v.* injection into animals bearing human COLO 205 tumor xenografts, "completely eliminated any measurable tumors within 2 weeks" and

"toxic side effects were minimal" (*Id.* at paragraph abridging pp. 8620-8621). Liu 1996 summarized the results as showing the conjugate to be "highly cytotoxic in vitro in an antigen-dependent and tumor cell-selective manner and produced long-term cures of mice bearing human colon tumor COLO 205 xenografts at doses that caused little toxicity" (*Id.* at 8622, right col). Finally, Chari 1998, a review article entitled "Targeted Delivery of Chemotherapeutics: Tumor-Activated Prodrug Therapy," characterizes the antibody-maytansinoid conjugates as "tumor-activated prodrugs (TAPs) which are non-toxic in circulation but are preferentially converted to active drugs upon binding to the tumor and subsequent internalization into the tumor cells" (**Ex. 1015**, at paragraph abridging pages 101-102).

The above results are clearly at odds with Dr. Sliwkowski's statement that "[a]t the time the invention was made, it would have been expected that the level of HER2 expression on normal cells would lead to unacceptable cytotoxic side-effects for such an immunoconjugate" (**Ex. 1028**, para 14). Moreover, Chari 1992 and Liu 1996 reported immunoconjugate dose-response curves (**Ex. 1012**, Fig.3 and **Ex. 1023**, Fig. 2) similar to those described in the '856 patent (**Ex. 1001**, Fig. 6) that belie the notion that the dose-response results reported in the '856 patent are in any way surprising or unexpected with respect to clinical likelihood of success as suggested in the Sliwkowski Declaration. ("Those

findings enhanced the likelihood that a therapeutic window could be achieved and that toxicity in a clinical setting could be managed...the present application addresses the unpredictability in the art as to whether a huMAb4D5-8-DM1 immunoconjugate would have struck an appropriate balance between antibody selectivity and potency of the cytotoxic agent") (**Ex. 1028**, para 14). Accordingly, Petitioner respectfully submits that the prior arts available before the priority date of the '856 patent provides a reasonable expectation of success for the huMAb4D5-8-DM1 immunoconjugate conjugate (**Ex. 1016**, para. 44).

C. No Unexpected Results

Accompanying the July 6, 2010 response (**Ex. 1027**) was a second Declaration by Barbara Klencke, M.D. ("the Klencke Declaration," **Ex. 1029**), which discusses the results of a Phase II clinical trial that was undertaken with "T-DM1," a huMAb4D5-8-maytansinoid conjugate within the scope of the present claims. The Klencke Declaration states that the objective response rate (ORR), which is the percentage of patients whose tumors shrank by at least 30% after treatment with T-DM1 was 32.7%, which "significantly exceeded that of current second-line therapies (23.7%), and well surpassed that of current third line therapies (12.4%)." Dr. Klencke characterized this result as "a better result than expected" (**Ex. 1029**, para 18)...[and as] fill[ing] a long felt but unresolved

need…for HER2-directed agents that treat metastatic HER2-positive breast cancer (**Ex. 1029**, para 24).

Unexpected results that are probative of non-obviousness are those that are "different in kind and not merely in degree from the results of the prior art." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). However, the increase in ORR from 23.7% to 32.7% ORR does not represent a "difference in kind" that is required to show unexpected results. *See In re Huang,* 100 F.3d 135, 139 (Fed.Cir.1996) (holding that claimed ranges must "produce a new and unexpected result which is different in kind and not merely in degree from results of the prior art"). Further, as confirmed by the Declaration of Dr. Rosenblum, such an increase is neither unexpected, nor surprising when considering the prior art teachings further described herein.

It should be noted that secondary considerations do "not always overcome a strong prima facie showing of obviousness." *Asyst Techs., Inc. v. Emtrak, Inc.,* 544 F.3d 1310, 1316 (Fed. Cir. 2008) (affirming judgment as a matter of law of obviousness). In this case, the secondary consideration evidence should not overcome a strong case of obviousness merely involving the substitution of a mouse ErbB2 antibody (*i.e.,* TA.1) with a humanized ErbB2 antibody, where the humanized ErbB2 antibody operates in a well-known manner.

Therefore , the immunoconjugate of Claims 1-8 of the '856 patent does not provide unexpected results "demonstrating that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" as alleged on page 10 of the July 6, 2010 response (**Ex. 1027**). According to the Declaration of Dr. Rosenblum, it is neither surprising nor unexpected that the claimed immunoconjugate would exhibit a significant inhibitory effect on tumor growth in the patient population described in the Klencke Declaration (**Ex. 1016**, 45-46).

VIII. CONCLUSION

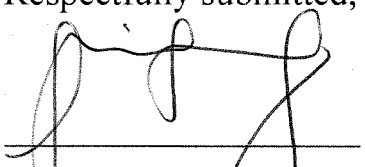
This is a textbook case of there being "an apparent reason to combine the known elements in the fashion claimed by the patent at issue" such that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1739, 1741 (2007).

For the foregoing reasons, the Petitioner respectfully requests that Trial be instituted and that Claims 1-8 of the '856 patent be canceled.

The undersigned further authorizes payment for any additional fees or credit of overpayment that might be due in connection with this petition to Deposit Account 50-2849.

Respectfully submitted,

Dated: May 1, 2014



Ping Wang, M.D., Esq.
Reg. No. 48,328
Attorney for Petitioner
Phigenix, Inc.

Andrews Kurth, LLP
Suite 1100
1350 I Street, N.W.
Washington, DC 20006
Phone - 202-662-2700
Fax - 202-662-2736

CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§ 42.6 (e) and 42.105 (a) on the Patent Owner by Express Mail of a copy of this Corrected Petition for *Inter Partes* Review at the below correspondence address of record for the '856 patent:

Sughrue Mion/IMMUOGEN

2100 Pennsylvania Avenue, NW

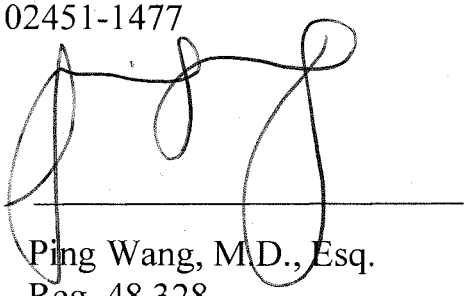
Washington, D.C., 20037

With Copy: ImmunoGen, Inc. Legal Department

830 Winter Street

Waltham, MA 02451-1477

Dated: May 1, 2014



Ping Wang, M.D., Esq.
Reg. 48,328
Attorney for Petitioner
Phigenix, Inc.

Andrews Kurth, LLP
Suite 1100
1350 I Street, N.W.
Washington, DC 20006
Phone - 202-662-2700
Fax - 202-662-2736