UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner

U.S. Patent No. 9,725,504 B2
Issue Date: August 8, 2017

Title: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

DECLARATION OF CINDY IPPOLITI, PHARM.D.

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I, Cindy Ippoliti, declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

A. Qualifications and Experience

1. My Curriculum Vitae, which contains information pertaining to my education, experience, and qualifications, as well as a list of my publications within at least the preceding 10 years, and publications on relevant subject matter is attached as **Exhibit A**.

2. I reside in West New York, New Jersey.

3. I have been retained by counsel for Petitioner to provide my expert opinion in connection with the above-captioned proceeding as set forth herein.

4. I am employed as the Enterprise Director of Clinical Pharmacy Services and Director of Oncology at New York Presbyterian, since April 2019 and January 2006, respectively.

5. I obtained a Bachelor of Science in Pharmacy from the Philadelphia College of Pharmacy and Science in 1985 and a Doctor of Pharmacy from the Philadelphia College of Pharmacy and Science in 1988.

6. I was first employed as a pharmacist in 1986 and have been continuously employed at world-class research hospitals ever since, holding

numerous positions in clinical pharmacy over the last thirty-five years.

7. I have published over fifty journal articles in the field of pharmacology with a focus on cancer and autoimmune diseases. I have received numerous research grants and have served as the study chairman or principal investigator for nineteen clinical trials. I have also given over forty presentations at various conferences and symposiums, many of which were related to drug therapies for hematologic disorders. My current research interests include hematology; I am a member of the American Society for Hematology.

8. As a co-investigator in clinical trials, my role typically involves data collection, data assessment, and authoring of study publications. Over the course of my career, I have also been involved in observing patients and documenting their reactions to therapies. As a former director of clinical trials, I also have experience providing administrative pharmacy oversight regarding the budget, personnel, and policies for various studies.

9. Through my many years of work in clinical pharmacy services, I have firsthand experience regarding handling vials of antibody drug units, understanding antibody drug doses and antibody formulations, the importance of hygienic and sterile clinical technique, and preparation of materials such as IV bags for intravenous dosing of antibody drugs to patients. I also personally participate in the

performance evaluation of pharmacists who compound these antibodies and observation of the administration of antibody drugs to patients in the hospitals in which I work. I was involved in clinical trials (and later administration in a hospital setting) of Rituxan, the first FDA-approved monoclonal antibody for the treatment of cancer, over 25 years ago. Many of the patients treated in these hospitals are PNH patients, and patients suffering from other maladies, who are receiving eculizumab (Soliris) by IV infusion.

10. I am being compensated at my usual consulting rate of $500 per hour for my work on this matter. I also am being reimbursed for reasonable and customary expenses associated with my work and testimony in this investigation. My compensation is not dependent upon my opinions or testimony or the outcome of this proceeding.

B. Materials Considered

11. The analysis that I provide in this Declaration is based on my education, research, and experience, as well as the documents I have considered. In forming my opinions, I have read and considered U.S. Patent No. 9,725,504 B2 ("'504 patent") **[EX1001]**.

12. I am aware that another expert, Jeffrey Ravetch, M.D., Ph.D., has

prepared an expert report in which he opines that the eculizumab antibody sequence recited as SEQ ID NOS:2 and 4 in the claims of the ’504 patent was anticipated and obvious as a pharmaceutical composition for use in treating PNH, in view of the disclosures of the prior art. I have reviewed Dr. Ravetch’s report and considered it in rendering the opinions in my declaration. (EX1003.)

13. I also understand that on February 28, 2019, Amgen challenged all claims of the ’504 patent in IPR2019-000739. (EX1024 & EX1026.) I also understand that the Board instituted that IPR, but that it was not completed due to the parties settling their case and the IPR terminating before the Board reached any final written decision.

14. I have cited to or considered the following additional documents in my analysis below:

Exhibit No.	Description of Document
1001	U.S. Patent No. 9,725,504 B2 issued to Leonard Bell et al. (filed Sept. 9, 2016, issued Aug. 8, 2017) (“’504 patent”)
1003	Declaration of Jeffrey V. Ravetch, M.D., Ph.D.
1004	U.S. Patent Application Publication No. 2003/0232972 A1 issued to Katherine S. Bowdish et al. (filed Dec. 2, 2002, published Dec. 18, 2003) (“Bowdish”)

Exhibit No.	Description of Document
1005	U.S. Patent No. 6,355,245 B1 issued to Mark J. Evans et al. (filed June 7, 1995, issued Mar. 12, 2002) ("Evans")
1007	U.S. Patent Application Publication No. 2005/0191298 A1 issued to Leonard Bell et al. (filed Feb. 3, 2005, published Sept. 1, 2005) ("Bell")
1008	Paul J. Tacken et al., *Effective induction of naive and recall T-Cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody*, 106 Blood 1278 (2005) ("Tacken")
1009	World Intellectual Property Organization International Publication No. WO 97/11971 issued to John P. Mueller et al. (filed Sept. 27, 1996, published Apr. 3, 1997) ("Mueller PCT")
1010	Thomas C. Thomas et al., Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv, 33 Molecular Immunology 1389 (1996) ("Thomas")
1011	Peter Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. Engl. J. Med. 552 (2004) ("Hillmen 2004")
1012	Anita Hill et al., *Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy*, 104 Blood 772a (2004) ("Hill 2004")
1013	Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 Blood 2559 (2005) ("Hill 2005")
1014	Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006")

Exhibit No.	Description of Document
1015	Neal S. Young et al., *Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study*, 108 Blood 290a (2006) ("Young")
1016	Peter Hillmen et al., *Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent*, 100 Blood 44a (2002) ("Hillmen 2002")
1017	Peter Hillmen et al., *Abstract# 1858: Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy*, 102 Blood 509a (2003) ("Hillmen 2003")
1024	*Amgen Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, Paper 15, Decision – Institution of *Inter Partes* Review (PTAB Aug. 30, 2019)
1026	*Amgen Inc. v. Alexion Pharmaceuticals*, IPR2019-00739, Paper 48, Termination – Due to Settlement After Institution of Trial (PTAB June 1, 2020)
1044	U.S. Patent Application Publication No. 2005/0271660 A1 issued to Yi Wang (filed May 11, 2005, published Dec. 8, 2005) ("Wang")
1052	Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012) ("Reichert")
1055	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
1056	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm

Exhibit No.	Description of Document
1057	ImClone Systems, Inc., Erbitux 2004 Package Insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125084lbl.pdf
1058	Genentech, Inc., Herceptin 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen092598lb.pdf
1059	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
1060	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
1061	Ann L. Daugherty & Randall J. Mrsny, *Formulation and delivery issues for monoclonal antibody therapeutics*, 58 Advanced Drug Delivery Reviews 686 (2006)
1063	Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product, European Agency for the Evaluation of Medicinal Products (2003)
1065	Health, United States, 2005 with Chartbook and Trends in the Health of Americans, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2005)

II. PERSON OF ORDINARY SKILL IN THE ART

15. I am informed by counsel that an assessment of claims of the ’504 patent should be undertaken from the perspective of a person of ordinary skill in the

art as of the earliest claimed priority date (i.e., the "time the invention was made"). For purposes of the '504 patent, I have assumed that date to be March 15, 2007, which is the date the earliest application in the patent family from which the '504 patent issued (Appl. Ser. No. 12/225,040) was filed. I am not aware of any claim by the patent owner that the claims of the '504 patent are entitled to an earlier date of invention, but I reserve the right to supplement this opinion if the patent owner were to later claim that the '504 patent was entitled to an earlier priority date.

16. I have been advised that to determine the appropriate level of a person having ordinary skill in the art, I may consider the following factors: (1) the types of problems encountered by those working in the field and prior art solutions thereto; (2) the sophistication of the technology in question, and the rapidity with which innovations occur in the field; (3) the educational level of active workers in the field; and (4) the educational level of the inventor. I am also informed that a person of ordinary skill in the art is presumed to be aware of all of the pertinent prior art.

17. The '504 patent relates to "[t]reatment of [PNH] patients by an inhibitor of complement." (EX1001, Cover.) The '504 patent discloses sequences for the heavy and light chains of such inhibitor of complement, the anti-C5 antibody eculizumab. It also discloses methods of treatment of disorders such as paroxysmal nocturnal hemoglobinuria ("PNH") using eculizumab, and clinical trials such as the

"TRIUMPH" and "SHEPHERD" trials studying eculizumab as a treatment for PNH. I provide a more complete overview of the '504 patent in **Part V** below. As noted above, I have extensive education and experience in the field of using antibodies as therapies and related issues of antibody formulation, dosing, and administration. I am familiar with the relevant skill set that would have been possessed by a hypothetical person of ordinary skill in the art ("POSA") at the time of the invention of the '504 patent (March 2007).

18. In my opinion and based on the subject matter of the '504 patent, the level of ordinary skill in the relevant art was high. I have reviewed Dr. Ravetch's statement of the level of ordinary skill in this field, and I agree with it and have applied it in reaching the opinions expressed in this declaration. Specifically, Dr. Ravetch opines (and I agree) that a POSA as of March 2007 would have knowledge of the scientific literature and have skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007. Such a person also would have knowledge of laboratory techniques and strategies used in immunology research, including practical applications. A POSA would have possessed an advanced degree in the biological sciences, such as an M.D. or a Ph.D., in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, and at least two years of

experience in the discovery, development, and design of therapeutic antibodies for use as potential treatment in human disease. A POSA could have also worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also upon specialized skills of team members, for example, a clinician, a doctor of pharmacy, and a formulation chemist who are part of a team may help solve a given problem.

19. As a doctor of pharmacy actively involved in multidisciplinary teams that develop and deliver biologic drugs, and having worked on clinical trials related to various antibody therapies, I would have advised a person having ordinary skill in the art as of March 2007. My analysis and opinions regarding the '504 patent are based on the perspective of an ordinarily skilled team member working with a person of ordinary skill in the art as of March 2007.

III. STATEMENT OF LEGAL PRINCIPLES

A. Claim Construction

20. I understand that a purpose of claim construction is to determine what a person of ordinary skill in the art would have understood the claim terms to mean. Claim terms are generally given their ordinary and customary meaning, which is the meaning that the term would have to a person of ordinary skill in the art in question

as of the earliest claimed priority date. I have interpreted all the claim terms in accordance with the ordinary and customary meaning of such terms as understood by one of ordinary skill in the art in 2007.

B. Obviousness

21. I understand that a patent claim is obvious if, as of the earliest claimed priority date, the invention recited in view of the claims would have been obvious to a person having ordinary skill in the field of the technology to which the claimed subject matter belongs.

22. I understand that the following factors should be considered in analyzing obviousness: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; and (3) the level of ordinary skill in the pertinent art. I also understand that certain other facts known as "secondary considerations" such as commercial success, unexplained results, long felt but unsolved need, industry acclaim or praise, simultaneous invention, copying by others, skepticism by experts in the field, and failure of others may be utilized as indicia of nonobviousness. I understand, however, that secondary considerations evidence must be connected, or have a "nexus," with the novel aspects of the invention claimed in the patent at issue in order to be relevant to the obviousness inquiry.

23. I understand that a reference qualifies as prior art for obviousness purposes when it is analogous to the claimed invention. The test for determining what art is analogous is: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.

24. I understand that a person of ordinary skill in the art is assumed to have knowledge of all prior art. I understand that one skilled in the art can combine various prior art references based on the teachings of those prior art references, the general knowledge present in the art, or common sense. I understand that a motivation to combine references may be implicit in the prior art, and there is no requirement that there be an actual or explicit teaching to combine two references. Thus, one may take into account the inferences and creative steps that a person of ordinary skill in the art would employ to combine the known elements in the prior art in the manner claimed by the patent at issue. I understand that one should avoid "hindsight bias" and ex post reasoning in performing an obviousness analysis. But this does not mean that a person of ordinary skill in the art for purposes of the obviousness inquiry does not have recourse to common sense.

IV. TECHNOLOGY AND FACTUAL BACKGROUND

A. By 2007, Therapeutic Antibodies Were Routinely Used as Pharmaceutical Compositions

25. By 2007, the FDA had approved more than a dozen antibodies, including several humanized antibodies, for therapeutic use in humans. (*See* EX1052, Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012), 002-03.) This included several still-widely prescribed antibodies, with which I was personally familiar before 2007, such as Avastin (EX1055), Campath (EX1056), Erbitux (EX1057), Herceptin (EX1058), Remicade (EX1059), Rituxan (EX1060).

26. These antibodies were commonly manufactured as pharmaceutical compositions that were formulated in sterile, preservative-free single use dosage forms and administered by intravenous ("IV") infusion. As explained in more detail below, it was by far the most common format for antibodies to be sold to pharmacy centers as single use dosage forms. Once a vial containing antibody drug substance is opened, sterility is considered compromised, and any remaining drug substance generally should not be stored for later administration because of the lack of sterility. Thus, drug companies know that pharmacies much prefer to receive drug in single use formats that can be completely used in a single administration event, thereby

avoiding any waste associated with discarding unused antibody drug substance. Similarly and relatedly, antibodies were commonly supplied in a preservative-free format, because again antibody drug vials should not be stored for long periods of time, and should not be stored at all after having been opened. Accordingly, there is little need for preservatives to be included in the antibody formulation, and preservatives are thus considered optional components for inclusion in antibody drug preparations. Finally, IV administration, almost always through an infusion as opposed to bolus injection, was (and is) by far the most common route of administration of antibody therapies.

B. By 2007, the Anti-C5 Antibody Eculizumab Was Known as a Treatment for PNH

27. Paroxysmal Nocturnal Hemoglobinuria, abbreviated PNH, is a disease in which a genetic mutation means that red blood cells undergo more frequent destruction by the complement system. (EX1007, U.S. Patent Application Publication No. 2005/0191298 issued to Leonard Bell et al. ("Bell"), [0005]; EX1013, Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 Blood 2559 (2005) ("Hill 2005"), 009.) Patients who suffer from PNH have sudden attacks ("paroxysms") in the night ("nocturnal") and have hemoglobin in the urine which causes a dark coloring

("hemoglobinuria"). (EX1007, [0007]; EX1013, 009.) Other common clinical symptoms of PNH are anemia, fatigue, thrombosis and pain. (EX1007, [0007]; EX1013, 009; EX1011, Peter Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. Engl. J. Med. 552 (2004) ("Hillmen 2004"), 004.)

28. Before 2007, it was understood that the negative symptoms suffered by PNH patients can be ameliorated by inhibiting the complement cascade pathway at the step at which the complement protein C5 is converted to C5a and C5b. Preventing cleavage of C5 results in complement inhibition that blocks the generation of C5a and formation of C5b-9, but leaves intact the aspects of the complement system that are upstream of C5, which are activities that are important for the clearance of microorganisms and immune system function. (EX1013, 009; EX1011, 004.) By 2007, three references – Bell, Hillmen 2004 and Hill 2005 – taught the use of pharmaceutical compositions with antibody formulations that are delivered intravenously to treat PNH patients. (EX1007, [0062], [0082]; EX1013, 010; EX1011, 005.)

29. Thus, before the March 15, 2007 priority date of the '504 patent, it was known that the anti-C5 antibody called eculizumab binds the complement protein C5 specifically and thereby prevents its cleavage, inhibiting C5 conversion.

(EX1013, 009.) For example, the Bell reference discloses results from a Phase 2 clinical trial that showed the successful treatment of eleven PNH patients using anti-C5 antibody. (EX1007, [0082].) Hillmen 2004 also reported results from the same clinical trial, stating that "[e]culizumab is safe and well tolerated in patients with PNH." (EX1011, 003.) Hill 2005 reported the results of a one-year follow-up extension study that evaluated the long-term safety and efficacy of eculizumab in PNH patients. (EX1013, 009.) Thus, all three publications—Bell, Hillmen 2004, and Hill 2005—reported that eculizumab was a useful treatment for PNH well before 2007. Several other prior art references also reported clinical trial results for eculizumab as a PNH treatment. (EX1014, Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006"); EX1015, Neal S. Young et al., *Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study*, 108 Blood 290a (2006) ("Young"); EX1012, Anita Hill et al., *Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy*, 104 Blood 772a (2004) ("Hill 2004"); EX1017, Peter Hillmen et al., *Abstract# 1858: Eculizumab, a C5 Complement-Blocking*

Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy, 102 Blood 509a (2003) ("Hillmen 2003"); EX1016, Peter Hillmen et al., *Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent*, 100 Blood 44a (2002) ("Hillmen 2002").)

V. THE '504 PATENT

A. Issued Claims

30. The '504 patent has ten issued claims:

> 1. A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 2. The method of claim 1, **wherein the pharmaceutical composition is administered by intravenous infusion**.
>
> 3. The method of claim 1, **wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment**.

4. The method of claim 1, **wherein the pharmaceutical composition is in a single unit dosage form**.

5. The method of claim 4, **wherein the single unit dosage form is a 300 mg single unit dosage form**.

6. The method of claim 1, **wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution**.

7. The method of claim 1, wherein the patient is anemic.

8. The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

(EX1001, 39:2-32 (emphasis added).)

31. My opinions in this declaration, as detailed below, pertain specifically

to the limitations of claims 2-6 underlined above.

B. Overview of the Specification

32. As noted above, the ’504 patent describes the use of a pharmaceutical composition comprising an anti-C5 antibody (such as eculizumab) for the treatment of PNH based on its ability to bind to complement C5 and inhibit its cleavage. The ’504 patent teaches that anti-C5 antibodies “are known,” and such antibodies disclosed in U.S. Patent Number 6,355,245 (Evans) “include a preferred” antibody “now named eculizumab.” (EX1001, 12:28-31.) The patent describes details of the Phase 3 “TRIUMPH” clinical trial in which eculizumab was evaluated in PNH patients. (*Id.*, 19:53-28:38.) The patent further provides details for the amino acid sequence of the heavy and light chains of the eculizumab antibody. This topic is a primary subject of Dr. Ravetch’s report.

33. As relevant here, the patent also provides details relating to the route of administration of eculizumab (IV infusion), the dose format (single use, sterile, preservative-free), the dosage level (between 5 mg/kg and 50 mg/kg), the dose unit (300 mg), and the formulation volume size and concentration (30 mL of a 10 mg/ml solution). (EX1001, 15:64-17:9.) The ’504 patent makes no claim of novelty with respect to any of these parameters or limitations, nor could it, since these were

entirely routine and conventional by 2007. Indeed, this section of the '504 patent refers to "Remington's Pharmaceutical Sciences" for formulations suitable for injection. (EX1001, 16:45-47.) Prior art references Bell, Evans, and Bowdish also refer to the same Remington's Pharmaceutical Sciences for techniques for formulations suitable for injection and administration. (EX1007, [0062]; EX1005, 18:33-35; EX1004, [0148].) Indeed, Remington's is the standard text for this subject matter, and further underscores that a POSA would understand the '504 patent to be relying only on conventional and routine means for administration of eculizumab as a therapy.

VI. APPLICATION OF THE PRIOR ART TO CHALLENGED CLAIMS

34. As explained above and in connection with my analysis below, I note that Dr. Ravetch opines as to the claim limitations relating to methods of treating PNH using the anti-C5 antibody defined with reference to SEQ ID NOS:2 and 4 by each of the claims, and concludes that those sequences were anticipated and obvious in view of the prior art. Further, Dr. Ravetch also opines that the claim limitations recited in claims 7-10 are obvious. Specifically, Dr. Ravetch's report lays out the following Grounds for unpatentability:

Ground	Claim(s)	Basis for Challenge
1	1-5, 7-10	Obvious over Bell (EX1007), Bowdish (EX1004), and Evans (EX1005) in view of Tacken (EX1008) and Mueller PCT (EX1009)
2	6	Obvious over Bell, Bowdish, Evans, and Wang (EX1044) in view of Tacken and Mueller PCT
3	1-5, 7-10	Obvious over Bell, Evans, and Mueller PCT in view of Tacken
4	6	Obvious over Bell, Evans, Mueller PCT, and Wang in view of Tacken
5	1-5, 7-10	Anticipated by Bell

35. The opinions expressed in my declaration are specific to the additional claim limitations recited in claims 2-6 that relate to the route of administration, dosage level and format, and formulation. Given the lack of inventiveness of SEQ ID NOS:2 and 4 as Dr. Ravetch has explained, in my opinion the route of administration, dosage level, dose form and formulation limitations added by claims 2-6 do nothing to rescue the patentability of the claims because they are routine, conventional, and uninventive. A POSA would have been motivated to apply these common techniques to the humanized antibody eculizumab (that is reflected by the SEQ ID NOS:2 and 4 in the challenged claims).

A. Brief Summary of Prior Art Discussed in this Declaration

1. Bowdish [EX1004]

36. **Bowdish** is a U.S. patent application that was published on December 18, 2003. Bowdish is titled "Rationally Designed Antibodies." I understand that Dr. Ravetch explains in his report that Bowdish, in combination with the Evans reference that is incorporated into Bowdish, teaches the complete amino acid sequence of SEQ ID NOS:2 and 4 recited in the challenged claims.

37. As relevant here, Bowdish also discloses that its antibodies can be formulated and administered as "pharmaceutical compositions." (EX1004, [0151].) These pharmaceutical compositions "can be administered intravenously" using known methods and "must be sterile." (*Id.*, [0148]-[0150].) Bowdish further states that "preservatives … can be incorporated according to accepted pharmaceutical practice," meaning that preservatives are optional in such pharmaceutical compositions. (*Id.*, [0150].)

2. Evans [EX1005]

38. **Evans** is a U.S. patent that issued on March 12, 2002, based on U.S. Application number 08/487,283. Evans is titled "C5-Specific Antibodies for the Treatment of Inflammatory Diseases." I understand that Dr. Ravetch explains in his

report that Evans provides the amino acid sequences for the variable regions of the heavy and light chains that correspond to the variable regions in SEQ ID NOS:2 and 4 recited in the challenged claims.

39. Evans also discloses that anti-C5 antibodies can be administered "in a variety of unit dosage forms." (EX1005, 17:60-61.) Evans states that typical doses for human patients are from 1 to 100 mg per kg and preferably 5 to 50 mg per kg of patient weight. (*Id.*, 18:7-11.) Evans also discloses that "[a]dministration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection," and that "[s]uch formulations must be sterile," and "may contain … preservatives[.]" (*Id.*, 18:29-43.)

3. Bell [EX1007]

40. **Bell** is a U.S. patent application that was published on September 1, 2005. Bell teaches that the anti-C5 antibody known as "h5G1.1-mAb (eculizumab)" is a "particularly useful" treatment for PNH. (EX1007, [0052], [0082].) Bell also discloses that "[t]he antibody h5G1.1" carried the "tradename eculizumab." (*Id.*, [0052].) Bell provides clinical results from a Phase 2 pilot study ("C02-001") in which eleven transfusion-dependent PNH patients were successfully treated with eculizumab, noting eculizumab "protected PNH type III [red blood cells] from

complement-mediated lysis, prolonging the cells survival." (*Id.*, [0083].) Bell notes that "[t]his protection of the PNH-affected cells reduced the need for transfusions, paroxysms and overall hemolysis in all patients in the trial." (*Id.*) Eculizumab also successfully decreased levels of lactate dehydrogenase and aspartate transferase (indicators of hemolysis). (*Id.*, [0085]-[0086], Fig. 1.) Bell explains that paroxysm rates "reduced by 93%," serum hemolytic activity was "completely blocked," and the need for transfusions was reduced with eculizumab. (*Id.*, [0087]-[0089], Figs. 3-6.) Bell also reports results from an extension study that showed that the reduction in transfusion need was durable, lasting over two years. (*Id.*, [0092].) Bell also discloses eculizumab pharmacodynamic data, improvement in overall patient quality of life, and a reduction in adverse symptoms associated with PNH. (*Id.*, [0093]-[0096], Figs. 8-10.)

41. Bell also teaches that "[m]ethods for the preparation of" h5G1.1 "are described in" Evans (EX1005) and Thomas (EX1010) and incorporates those disclosures "in their entirety." (EX1007, [0052].)

42. In addition, Bell teaches that the anti-C5 antibody formulations "suitable for injection" "must be sterile" and "may contain … preservatives[.]" (EX1007, [0062].) Bell also teaches that the patients in its Phase 2 study received a weekly 600mg intravenous infusion of eculizumab for four weeks, and a

maintenance dose in the form of "900mg of eculizumab 1 week later then 900 mg on a bi-weekly basis." (*Id.*, [0082].)

4. Tacken [EX1008]

43. **Tacken** is a journal article that was published in August 15, 2005. I understand that Dr. Ravetch explains in his report that the Tacken publication provides important disclosures about the amino acid structure of the heavy chain of eculizumab. I do not rely on Tacken for the opinions expressed in my report, other than to note that Dr. Ravetch relies on it in reaching his opinions.

5. Mueller PCT [EX1009]

44. **Mueller PCT** is an international patent application. I understand that Dr. Ravetch explains in his report that Mueller PCT discloses the sequence of eculizumab's hybrid IgG2/IgG4 heavy chain constant region, and methods of how to make and use an antibody with this hybrid constant region. I do not rely on Mueller PCT for the opinions expressed in my report, other than to note that Dr. Ravetch relies on it in reaching his opinions.

6. Wang [EX1044]

45. **Wang** is a U.S. patent application that was published on December 8, 2005. Wang relates to "methods and compositions" for antibody formulations, such

as eculizumab, that inhibit "activation of the complement system." (EX1044, Abstract, [0004].) Wang expressly references the Evans document described above and identifies the anti-C5 antibody "eculizumab" as a preferred embodiment. (*Id.*, [0004], [0011], [0067].)

46. Wang further discloses that the formulations of anti-C5 antibody, such as eculizumab formulations, "may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." (EX1044, [0067].) Wang provides examples of formulations that have eculizumab concentrations ranging from 1 mg/ml to 30 mg/ml while maintaining the effectiveness and integrity of the antibody. (*Id.*, Fig. 10, [0025], [0170]-[0173].)

B. Grounds 1-4: Claims 2-6 Are Obvious

47. As noted above in Part V, independent claim 1 of the '504 patent recites an anti-C5 antibody comprising the same SEQ ID NOS:2 and 4. In Ground 1 discussed in his report (EX1003, Part VI.B.1) and as set forth in Paragraph 34 above, Dr. Ravetch opines that these sequences were obvious over the teachings of Bell, Bowdish and Evans in view of Tacken and Mueller PCT. In Ground 3 discussed in his report (EX1003, Part VI.D.1) and as set forth in Paragraph 34 above, Dr. Ravetch opines that these sequences were obvious over the teachings of Bell, Evans, and

Mueller PCT in view of Tacken. Claims 2-6 depend from claim 1.

48. In my opinion, the remaining limitations of claims 2-6 of the '504 patent regarding route of administration, antibody dosage level, dose forms and formulation were trivial and uninventive, and indeed were expressly disclosed in the prior art. I discuss each of these limitations and the rationale for my obviousness opinions further below.

1. Claim 2: "intravenous infusion"

49. Claim 2 recites that the pharmaceutical composition is administered by intravenous infusion. Bell, Bowdish and Evans disclose that the pharmaceutical composition is administered intravenously. (*See* EX1007, [0062], [0082]; EX1004, [0148]-[0151]; EX1005, 18:29-43.) By 2007, a POSA would have known that it was routine and conventional to administer therapeutic antibodies such as eculizumab intravenously.

2. Claim 3: "a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment"

50. Claim 3 recites that the pharmaceutical composition is administered at "a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment." As noted above, Bell reports results from the eleven patient Phase 2 clinical trial

in which PNH patients were dosed with eculizumab using an initial 600 mg dose phase given weekly for four weeks followed by a maintenance dose of 900 mg dose given bi-weekly. (EX1007, [0082].) The CDC (Centers for Disease Control) has reported that the average body weight of adult females was 74 kg and the average body weight of adult males was 87 kg in the U.S. (EX1065, 061.) Based on this, Bell's 600 mg is equal to a dose of 8.1 mg/kg for an average adult female and 6.9 mg/kg for an average adult male. And Bell's 900 mg is equal to a dose of 12.2 mg/kg for an average adult female and 10.3 mg/kg for an average adult male. Thus, in Bell's study, patients received doses between 6.9 mg/kg and 12.2 mg/kg, all of which fall within the claimed range of between 5 mg/kg and 50 mg/kg.

51. Further, Evans teaches that anti-C5 antibodies are typically dosed from 1 to 100 mg per kg, "preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment." (EX1005, 17:60-18:13.) Accordingly, a POSA would have been motivated to administer eculizumab at dose levels between 5 mg/kg to 50 mg/kg. A POSA would have also had reasonable expectation of success in view of Bell's disclosures that doses in the range of 5-50 mg/kg had successfully treated PNH.

3. Claim 4: "single unit dosage form"

52. Claim 4 recites that the pharmaceutical composition is in a "single unit dosage form," and claim 5 further recites that that single unit dosage form is a dose of 300 mg. Claim 6 recites a "300 mg single-use formulation" as well.

53. As noted above, Bell reported a study in which eculizumab was dosed at 600 mg and 900 mg. (EX1007, [0082].) Bell also discloses that all doses were delivered by intravenous infusion. (*Id.*) Bell further teaches that antibodies can be administered "in a variety of unit dosage forms." (*Id.*, [0058].) A POSA would have known that single-use dosage units are preferred for use in organized health care settings such as hospitals, and especially in contexts such as intravenous infusion in which sterility must be maintained. As examples, each of the recombinant antibodies approved for human use that I discussed above was provided in a single-use dosage form before 2007. (EX1055 (Avastin), 002; EX1056 (Campath), 002; EX1057 (Erbitux), 001; EX1058 (Herceptin), 001-02; EX1059 (Remicade), 001; EX1060 (Rituxan), 001.) Thus, a POSA would have been motivated to prepare the antibody recited in the challenged claims as a pharmaceutical composition that is a single-use dosage form.

4. Claim 5: "300 mg single unit dosage form"

54. Claim 5 is almost the same as claim 4, but merely specifies that the dosage form be of a 300 mg amount. This was obvious.

55. In light of Bell's express teachings to employ a regimen consisting of 600 mg and 900 mg doses of eculizumab, a POSA would have been motivated to choose a 300 mg single-use dosage form. This would best support convenience and scaling as necessary to the needed 600 or 900 mg dose amounts – for example, a patient needing a 600 mg dose would receive two vials, while a patient needing a 900 mg dose would receive three vials. Making a larger single size whereby all of the antibody drug substance would not necessarily be used in a single administration session, would unnecessarily create a situation causing waste of costly antibody treatments. A pharmacy also would not prefer to stock (nor, presumably, would a drug company prefer to make), two different vial amounts of 600 and 900 mg each. This would unnecessarily complicate antibody supply services, inventory tracking, and also unnecessarily create the risk of an incorrect dose (too high or too low) being given to a patient, if a vial containing the incorrect amount was accidentally selected. Thus, a POSA would have been motivated to choose a single-use dosage form of 300 mg.

5. Claim 6: "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution"

56. Claim 6 recites that the antibody formulation is "sterile," and "preservative free." Each of Bell, Bowdish and Evans teach that formulations of anti-C5 antibodies, such as eculizumab, "must be sterile." (EX1007, [0062]; EX1004, [0150]; EX1005, 18:29-43.)

57. Bell and Evans also expressly disclose that the antibody formulations optionally "**may** contain … preservatives[.]" (EX1007, [0062]; EX1005, 18:29-43 (emphasis added).) Bowdish also discloses that "preservatives … **can** be incorporated according to accepted pharmaceutical practice." (EX1004, [0150] (emphasis added).) Thus all three references—Bell, Evans, and Bowdish—teach that use of preservative is optional in the formulation, thus teaching the "preservative free" limitation of the claims. Similarly, the '504 patent specification relates that preservatives are an optional component of the antibody formulation, using the same permissive "may" language that is used in the prior art; indeed the disclosure in the '504 patent appears to have been copied *verbatim* from the prior art Bell and Evans references, and cite the same standard "Remington's Pharmaceutical Sciences" for formulations suitable for injection. (*Compare* EX1001, 16:45-55, *with* EX1007, [0062]; EX1005, 18:33-43.) These teachings also agreed with common

pharmaceutical practice regarding antibody formulations in 2007. Indeed, some regulatory guidance such as from the EMEA indicated that preservatives should not be used in the formulation of medicines unless "absolutely necessary," due to the additional risk of harm to patients associated with the preservative agents. (*See* EX1063, 002, 009-10.) This same guidance states that medicines made without preservatives should not be prepared as multi-dose preparations, for the obvious reason of contamination due to loss of sterility. (*Id.*) Consistent with this guidance, commonly prescribed antibodies approved before 2007 were provided in single-use, sterile, preservative free formulations. (EX1052, 002-03; EX1055 (Avastin), 002; EX1056 (Campath), 002, 013; EX1057 (Erbitux), 001; EX1058 (Herceptin), 001-02; EX1059 (Remicade), 001; EX1060 (Rituxan), 001.)

58. I addressed the 300 mg limitation in the context of claim 5. (*See supra* ¶55.) Claim 6 also recites a formulation that is 30 ml of a 10 mg/ml antibody solution. By 2007, it was commonplace for antibody therapies to be supplied in a liquid solution that could easily be drawn into a syringe and added to IV bags for infusion. The Wang reference specifically discusses eculizumab formulations and teaches that eculizumab could be successfully and stably formulated in an aqueous solution at concentrations in the range of 1 to 30 mg/ml, which includes the concentration of 10 mg/ml. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173].) I

note that one of the concerns of the Wang authors was the development of a formulation for nebulization for delivery via inhalation, but this would not detract from a POSA's understanding that Wang teaches the stable formulation of eculizumab in aqueous solution at concentrations ranging from 1 to 30 mg/ml. Indeed, the same aqueous or liquid solutions are used for intravenous infusions as well.

59. A POSA also would have known that 10 mg/ml was well within the known range of concentrations of several FDA-approved antibodies. (EX1061, 014 (Table 1); EX1056 (Campath), 013 (10 mg/ml); EX1057 (Erbitux), 001 (2 mg/ml); EX1058 (Herceptin), 001-02 (21 mg/ml); EX1059 (Remicade), 001 (10 mg/ml); EX1060 (Rituxan), 001 (10 mg/ml).) Thus, given the desirability of supplying eculizumab as a 300 mg single-use dose amount as discussed above, and based on simple arithmetic, it would have been obvious for a POSA to use 30 ml of 10 mg/ml solution to administer the desired single-use dose of 300 mg. A POSA would also consider it advantageous to have the total supplied volume of the antibody drug substance be 30 ml – neither such a small volume that there would be concern about successfully drawing all the drug substance into a syringe, nor such a large volume as to be impractical to draw using a standard syringe or impractical to dilute into an IV solution for infusion into the patient.

6. Manner, Motivation, and Rationale for Combination

60. As discussed above, all three of Bell, Bowdish and Evans expressly teach antibody formulations and compositions that match claim limitations of claims 2-6. (*See* EX1004, [148]-[151]; EX1005, 17:60-18:43; EX1007, [0062], [0082].) A POSA would also have considered Wang clearly pertinent because of its express disclosures about eculizumab formulations and compositions. (EX1044, [0004], [0011], [0067].)

61. A POSA would also have had a reasonable expectation of success in arriving at the recited characteristics of the pharmaceutical compositions in claims 2-6, because as I discussed above, the prior art expressly discloses these characteristics specifically in the context of the anti-C5 antibody eculizumab, as opposed to antibodies or drugs in general. Further, Wang expressly teaches stable eculizumab formulations at concentrations as high as 30 mg/ml. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173].) Thus, a POSA would have had a reasonable expectation of success that eculizumab prepared at a concentration of 10 mg/ml would be a stable pharmaceutical composition suitable for therapeutic use, and would have had no concerns regarding aggregation at that concentration of antibody in solution. For example, antibody drugs for administration by IV infusion that are prepared in concentrations from 1 to 10 mg/ml have been described as "medium

protein concentration" which are "not dramatically affected by adherence or aggregation losses." (*See* EX1061, 009.) And, as noted above, even when considered in the context of antibody drugs in general, the route of administration, dosage levels, dose form and formulation limitations of claims 2-6 are entirely routine and conventional. A POSA also would not have had any reason to doubt that the teachings of the prior art and the experiences of drug developers with already-approved therapeutic antibodies would apply to eculizumab. Eculizumab, as discussed above, is a recombinant humanized antibody, and in that respect is highly similar to other already-approved antibodies such as Avastin (bevacizumab), Herceptin (trastuzumab), and Campath (alemtuzumab).

VII. NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

62. As explained in Part III.B, I understand that "secondary considerations" may be used as indicia of nonobviousness, provided that any such consideration has a nexus to the invention as claimed. I also understand that any secondary considerations evidence that is not both claimed and novel cannot have a nexus to the claimed invention. I am not aware of any secondary considerations of nonobviousness that would apply to the uninventive dose form and formulation limitations I discuss in my report. Accordingly, it is my opinion that there is no

evidence for secondary considerations of nonobviousness of the challenged claims. I reserve the right to rebut any evidence of secondary considerations that Alexion may assert in this proceeding.

VIII. CONCLUSION

63. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in this proceeding. If required, I will appear for cross-examination at the appropriate time.

64. I hereby declare that all statements made herein of my own knowledge are true and that all statements are made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001.

Respectfully submitted,

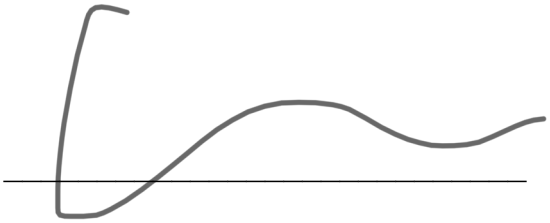

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EXHIBIT A

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Ippoliti C, Przepiorka D, Mehra R, et al. Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. **J of Urology** 1995;46:811-815.

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Przepiorka D, Madden T, **Ippoliti C**, et al. Dosing of thiotepa for myeloablative therapy. **Canc Chemother and Pharmacol** 1995;37:155-160.

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Przepiorka D, Dimopoulos M, Smith T, **Ippoliti C**, et al. Thiotepa, busulfan and cyclophosphamide

as a preparative regimen for marrow transplantation: Risk factors for early regimen-related toxicities. **Ann Hematol** 1994;68:183.

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Ippoliti C, Przepiorka D, Giralt S, et al. Low-dose nonglycosylated rhGM-CSF is effective for the treatment of delayed hematopoietic recovery after autologous marrow or peripheral blood stem cell transplantation. **Bone Marrow Trans** 1993;11:55-59.

Ippoliti C, Przepiorka D, Smith T, et al. Adverse effects of nonglycosylated rhGM-CSF in marrow transplant recipients. **Clinical Pharm** 1993;12:183-188.

Ippoliti C, Williams L, Huber S. Rapid infusion of concentrated intravenous immunoglobulin in bone marrow transplantation. **Clinical Pharmacy** 1992;11:1022-1026.

BOOK

Editor and Author for Supportive Care in Bone Marrow Transplantation, Summit Publication, 2008 (translated in English and Turkish).

JOURNAL REVIEW

Clinical Oncology Pharmacist, 2008-2012

ABSTRACTS

Przepiorka D, Ippoliti C, Khouri I, et al. Tacrolimus and mini-methotrexate for prevention of acute graft-vs-host disease (GVHD) after HLA-nonidentical marrow or blood stem cell transplantation. **ASBMT**

Przepiorka D, Ippoliti C, Khouri I, et al. Allogeneic transplantation for advanced leukemia: improved short-term outcome with blood stem cells and tacrolimus. **ASTP** 1996;#316.

Bugazia N, Ippoliti C, Gajewski J, et al. Octreotide (Sandostatin) in the management of graft-versus-host disease diarrhea. **Blood Cell and Marrow Transplants** 1996;#123.

Przepiorka D, Kernan N, Stein L, Ippoliti C, et al. Humanized Anti-Tac for treatment of visceral or steroid-refractory acute graft-versus-host disease. **Blood Cell and Marrow Transplants** 1996;#328.

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Przepiorka D, Gajewski J, Ippoliti C, et al. The combination of partial T-cell depletion and immunotoxin is optimal GVHD prophylaxis after MUD BMT. **ASBMT** 1995;71:114.

Ippoliti C, Morgan A, Przepiorka D, et al. Foscarnet for prevention of CMV in allogeneic marrow transplant recipients unable to receive ganciclovir. **Blood** 1994;84:711(no. 2831).

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Ippoliti C, Przepiorka D, Mehra R, et al. Dose escalation study of carboprost for hemorrhagic cystitis (HC) after bone marrow transplantation (BMT). **Journ Cell Biochem** 1994;18B:

Nath R, Przepiorka D, Ippoliti C, et al. Phase I-II study of high-dose thiotepa, busulfan and cyclophosphamide (TBC) with autologous BMT for high-risk lymphoma. **Blood** 1993;82(supp 1):536a(2133).

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Madden T, Ippoliti C, Johansen M, et al. A phase I pharmacokinetic (PK) evaluation of high-dose thiotepa with Marrow transplantation. **ACCR** 1993.

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Przepiorka D, Ippoliti C, Ownby K, et al. A phase I study of high-dose thiotepa, busulfan and cyclophosphamide with allogeneic marrow transplantation. **Blood** 1992;80, No 11 (supp 1):337a(1339).

Wood J, Przepiorka D, Kessler M, Ippoliti C, et al. The monoclonal antibody HA-IA as adjunctive therapy for immunocompromised patients with septic shock. **J Cell Biochem** 1992;216(supplement 16A):216(D 619).

Dimopoulos T, Przepiorka D, Ippoliti C, et al. High-dose thiotepa, busulfan and cyclophosphamide with autologous marrow transplantation: Toxicities of three different dose schedules. **ASCO** abstract #1332, 1992.

Przepiorka D, von Wolff B, Ippoliti C, et al. Anti-CD5 ricin A chain immunotoxin decreases acute graft-versus-host disease (GVHD) after unrelated donor marrow transplantation (MUD BMT). **Exp Hematology** 1992;20:709(17).

Ippoliti C, Przepiorka D, Giralt S, et al. Low-dose nonglycosylated rhGM-CSF if effective for the treatment of delayed engraftment following autologous bone marrow transplantation. **Blood** 1991;78(supplement).

RESEARCH GRANTS

$10,000 educational grant evaluating drug interactions between HIV medications and chemotherapueutic agents to treat lymphoma.

$7000 educational grant to evaluate efficacy of octreotide in GVHD diarrhea.

$100,000 research grant to study efficacy and toxicity of granisetron in BMT recipients.

$5,000 educational grant from Bristol-Myers for antibiotic studies in BMT.

$10,000 from Upjohn Pharmaceuticals to determine thiotepa and tepa pharmacokinetics in marrow transplant recipients.

$40,000 educational grant from Alpha Therapeutics for IVIG studies.

PROTOCOLS/RESEARCH

Decitibine for AML: Is continued therapy beneficial?, **Co-investigator**

Clag +/- M for the treatment of relapsed and refractory AML, **Investigator**

Outcome of patients who develop HHV-6 post allogeneic stem cell transplantation, **Co investigator**

MUE evaluating rasburicase in cancer patients at NYP, **Investigator**

Management of BK Virus in recipients of allogeneic stem cell transplantation, **Co investigator**

Toxicity of Pegylated Asparaginase in the Elderly, **Investigator**

KGF for the treatment of refractory GI graft versus host disease. **Co investigator**

Octreotide versus loperamide for the initial symptomatic management of graft-versus-host disease induced diarrhea. **principal investigator**

Aerosolized Amphotericin B for the Prevention of Fungal Pneumonia in Allogeneic Transplant Recipients. **principal investigator**

Pilot Study to Determine the Efficacy and Toxicity of Octreotide in the Treatment of Graft-Versus-Host Diarrhea. **principal investigator**

Standard Practice Protocol of Granisetron for Antiemetic Control in BMT Patients Receiving Highly Emetogenic Chemotherapy with or without Total Body Irradiation. **principal investigator**

Dose Escalation Study of Carboprost Tromethamine for the Treatment of Hemorrhagic Cystitis in

BMT Patients. **study chairman**

A Standard Practice Protocol for the Use of Foscarnet in Bone Marrow Transplant Patients With Presumed Herpesviriae Infections. **study chairman**

A Pilot Study for the Use of Foscarnet for Viral Prophylaxis After Allogeneic Marrow Transplantation. **study chairman**

Phase I Study of Soluble IL-1 Receptor in Patients With Acute GVHD.
co-investigator/pharmacokinetic responsibility

Emergency Use of Xomazyme-CD5 Plus for Moderate to Severe Acute GVHD Unresponsive to Systmeic Therapy With Steroids. **Co-investigator.**

A Phase I-II Study of High-dose Thiotepa, Busulfan and Cyclophosphamide With Allo/Auto BMT for Hematologic Malignancies. **co-ivestigator/pharmacokinetic responsibility**

The Compassionate Use of Granulocyte-macrophage-colony Stimulating Factor in Neutropenic Patients. **principal investigator**

Evaluation of the Stability and Tolerability of Concentrated Intravenous Immunoglobulin in BMT Patients. **principal investigator**

SELECTED PRESENTATIONS

"New Agents in Oncology" APAO Annual Meeting, Austin, TX

"Management of ALL", Pediatric Oncology Monthly Meeting, Dallas, TX

"Advocacy in Pharmacy", NYSHP Student Seminar, NY,NY

"Managing Nausea and Vomiting" National Meeting of Physician Assistants, NY, NY

"What's Hot in BMT Pharmacy" ASBMT Annual Nursing Meeting, San Diego, CA

"Medication Safety: Still an Issue?" New Perspectives in Oncology Practice, NY, NY

"Critical Care Issues in the Oncology Patient" HOPA Conference, Orlando, FL

"Use of Sirolimus / Tacrolimus for the Management of Chronic Graft Versus Host Disease" ASBMT Pharmacist Meeting, Honolulu, Hawaii

"Management of Transplant-related Toxicities", Bone Marrow Transplantation Conference, Kansas City, MO.

"Advances in the management of Graft Versus Host disease" Pharmacy Symposium, Houston, TX

"Use of Liposomal Amphotericin B in the Management of Fungal Infections", ASHP Midyear Clinical Meeting, Atlanta, GA

"Management of Fungal Infections in Transplant Recipients", Houston, TX

"Treatment of Respiratory Viral Infections in the Transplant Recipient", Viral Conference, Dallas, TX.

"Advances in Drug Therapy", 1997 Blood Cell and Marrow Transplantation Multidisciplinary Symposium, Dallas, TX.

"Aerosolized Amphotericin-B for the Prevention of Fungal Pneumonia in Allogeneic Transplant Recipients", Keystone Symposia on Blood and Marrow Transplantation, Keystone, CO.

"Octreotide in the Symptomatic Management of GI Graft-Versus-Host Disease Diarrhea", Keystone Symposia on Blood and Marrow Transplantation, Keystone, CO.

"Management of Chemotherapy-induced Diarrhea", ONS Meeting, San Antonia, TX.

"Developing Clinical Pharmacy Services in BMT", MDACC Annual Pharmacy Symposium, Houston, TX.

"Bone Marrow Transplantation: A Comprehensive Review", BMT Symposium, Forrest Green General Hospital, Hattiesburg, MS.

"Pharmacology of Cancer Chemotherapy", part of Medical Oncology Board Review Course, Houston, TX.

"Tacrolimus for the Prevention and Treatment of Graft Versus Host Disease", part of educational symposia sponsored by Fugisawa.

"Management of Bone Marrow Transplant Related Complications" Harlingen, TX.

"Management of Aplastic Anemia and other Blood Dyscrasias" University of Colorado School of Pharmacy, Pharm.D. therapeutics course.

"Graft-Versus-Host Disease" University of Houston College of Pharmacy, Immunology elective course.

"New Developments in Biotechnology" Little Rock Arkansas Society of Hospital Pharmacists, Little Rock, AR

"Bone Marrow Transplantation: A Clinical Case Study" part of an education conference, Issues in Transplantation: A Multidisciplinary Approach, Houston, TX

"Novel Uses of Erythropoietin" Methodist Hospital, Houston, TX

"A Clinical Perspective on the Colony-Stimulating Factors in Cancer Patients" M.D. Anderson Cancer Center Annual Pharmacy Symposium, Houston, TX

"Rapid Infusion of Concentated IVIG in BMT Patients" ASHP Annual Meeting, San Diego, CA

"Use of IVIG in BMT Patients" Alpha Therapeutics Annual Meeting, San Diego, CA

"The Colony-Stimulating Factors in Cancer Patients" part of education symposium on cancer management, Houston, TX

"Fluconazole: A Clinical Perspective" M.D. Anderson Cancer Center Annual Pharmacy Symposium, Houston, TX

"Transplantation Versus Standard Chemotherapy in the Treatment of Leukemias" M.D. Anderson Cancer Center Annual Nursing Symposium, Houston, TX

"Management of Infections in the Neutropenic Patient" University of Houston School of Nursing, Master's Program, Houston, TX

"Carboplatin: A Cisplatin Alternative or Replacement?" M.D. Anderson Cancer Center Pharmacy Symposium, Houston, TX

"Ganciclovir: Wonder Drug for Cytomegalovirus?" M.D. Anderson Cancer Center Pharmacy Symposium, Houston, TX

"Interleukin 3 in the Management of Aplastic Anemia" Southwest Leadership Conference, Dallas, TX

"New Immunologic Approaches to Graft Versus Host Disease" Shands Hospital, Gainesville, FL

"Therapeutic Aspects of Bone Marrow Transplantation" North Dallas Society of Hospital Pharmacists, Dallas, TX

"Impact of Diagnosis Related Groups on Pharmacy Practice" U.T. M.D. Anderson Cancer Center, Houston, TX

TEACHING/EDUCATION

Member, Institutional Review Board, Cornell Medical Center 2007 – 2012
Member, Chemotherapy Safety Committee, 2007-present
Co-chair, Heme/Onc Subcommittee, 2006-present
Member, Residency Committee (RAC), 2007 – present
Member, BMT QI committee, Cornell, 2007-present
Member, order set committee, NYP
Member, Antibiotic Task Force, MDACC, 1998.
Member, Antiemetic Task Force, MDACC, 1998

Member, Clinical Ethics Committee and Consult Service, MDACC, 1995
Adjunct Assistant Professor, University of Houston School of Pharmacy
Adjunct Assistant Professor, PCPS
Co-chairman, ASBMT Annual Pharmacists meeting 2003 – 2008

PROFESSIONAL AFFILIATIONS

American Society for Blood and Marrow Transplantation
New York State Pharmacist Association
American Society for Hematology
Kappa Epsilon Professional Pharmaceutical Fraternity

REFERENCES AVAILABLE UPON REQUEST