UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2023-00999
U.S. Patent No.
9,725,504 B2

REPLY DECLARATION OF JEFFREY V. RAVETCH, M.D., PH.D.

TABLE OF CONTENTS

Page

I. INTRODUCTION 4

A. Background 4

B. Materials Considered 5

II. OPINIONS RESPONDING TO ALEXION'S RESPONSE 18

A. Alexion Relied on Expert Testimony Recycled from a Different Legal Proceeding 18

B. Alexion Mischaracterizes the Clear Teachings of Its Own Prior Art and the Import of Its Admissions 20

C. Ground 1: Claims 1-5 and 7-10 Are Obvious over Bell, Bowdish, and Evans in View of Tacken and Mueller PCT 28

1. No Dispute that the Prior Art Taught Eculizumab Was an Effective PNH Treatment; No Dispute that the Prior Art Sequences Read on the Challenged Claims 28

2. A POSA Would Have Followed Samsung's Obviousness Rationale 28

3. A POSA Would Have Had a Reasonable Expectation of Success 35

D. Ground 3: Claims 1-5 and 7-10 Are Obvious over Bell, Evans, and Mueller PCT in View of Tacken 45

1. A POSA Would Have Followed Samsung's Obviousness Rationale 45

2. A POSA Would Have Had a Reasonable Expectation of Success 54

Samsung Bioepis Exhibit No. 1103
Samsung Bioepis Co., Ltd. v. Alexion Pharmaceuticals, Inc., IPR2023-00999
Page 2

TABLE OF CONTENTS

(continued)

Page

E. Grounds 2 and 4: Claim 6 Is Obvious over the Combinations of Grounds 1 and 3 Further Combined with Wang 58

F. Ground 5: Claims 1-5 and 7-10 Are Anticipated by Bell 67

G. Alexion Failed to Show Any Secondary Considerations of Non-Obviousness.....69

III. CONCLUSION.....72

Samsung Bioepis Exhibit No. 1103
Samsung Bioepis Co., Ltd. v. Alexion Pharmaceuticals, Inc., IPR2023-00999
Page 3

I, Jeffrey V. Ravetch, declare as follows:

I. INTRODUCTION

A. Background

1. I am the same Jeffrey V. Ravetch, M.D., Ph.D. who provided a declaration in support of the IPR Petition of Samsung Bioepis ("Samsung") in this matter relating to Alexion's U.S. Patent No. 9,725,504. Apart from updating my CV as discussed next, I incorporate by reference my previous statement of qualifications and experience. (EX1003, ¶¶1-14.)

2. My updated Curriculum Vitae, which contains information pertaining to my education, experience, and qualifications in the field of immunology, microbiology, cellular biology, and molecular genetics, 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**.

3. I submit this declaration in response to the arguments and opinions submitted by Alexion and its experts Drs. Casadevall and Trout.

4. I am being compensated at my usual consulting rate of $1,250 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 proceeding. My compensation is not dependent upon my opinions or testimony or the outcome of

this proceeding.

B. Materials Considered

5. 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 addition to the documents discussed in my previous declarations, I have also read and considered the documents added to the table below (which comprehensively includes the documents that were listed in my previous declaration):

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")
1002	Prosecution History for U.S. Patent No. 9,725,504 B2
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")
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")
1006	John P. Mueller et al., *Humanized Porcine VCAM-Specific Monoclonal Antibodies with Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding to Porcine Endothelial Cells*, 34 Molecular Immunology 441 (1997) ("Mueller 1997")
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")

Exhibit No.	Description of Document
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 ("Hill 2005")
1014	Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006")
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*

Exhibit No.	Description of Document
	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")
1018	Excerpts from *Recommended INN List 49, International Nonproprietary Names for Pharmaceutical Substances*, 17 WHO Drug Information 115, World Health Organization (2003)
1019	*Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, Programme on International Nonproprietary Names (INN), Division of Drug Management & Policies, World Health Organization, Geneva (1997)
1020	Alexion Press Release, *Alexion Issued Key C5 Complement Inhibitor Patent for Inflammatory Diseases* (Mar. 15, 2002), https://web.archive.org/web/20030621141230/http://www.alxn.com/products/index.cfm
1021	World Intellectual Property Organization International Patent Publication No. WO 2005/007809 A2 issued to Russell P. Rother et al. (filed May 28, 2004, published Jan. 27, 2005)
1022	World Intellectual Property Organization International Patent Publication No. WO 2005/110481 A2 issued to Russell P. Rother et al. (filed May 16, 2005, published Nov. 24, 2005)
1023	Mariana Kaplan, *Eculizumab Alexion*, 3 Curr. Opin. Investig. Drugs 1017 (2002)
1024	*Amgen Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, Paper 15, Decision – Institution of *Inter Partes* Review (PTAB Aug. 30, 2019)

Exhibit No.	Description of Document
1025	*Amgen Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, Paper 22, Patent Owner Response Pursuant to 37 C.F.R. § 42.120 (PTAB Nov. 22, 2019)
1026	*Amgen Inc. v. Alexion Pharmaceuticals*, IPR2019-00739, Paper 48, Termination – Due to Settlement After Institution of Trial (PTAB June 1, 2020)
1027	Opposition File History for European Patent No. 1 720 571 B1
1028	File History for European Patent No. 3 167 888
1029	Excerpt from the File History for U.S. Patent Application No. 11/127,438, Amendment in Response to Non-Final Office Action (Aug. 2, 2011)
1030	Application for Extension of Patent Term under 35 U.S.C. § 156 and 37 CFR § 1.740, U.S. Patent No. 6,355,245, Alexion Pharmaceuticals (May 11, 2007)
1031	Certificate Extending Patent Term, U.S. Patent No. 6,355,245 (June 11, 2010)
1032	Excerpt from the File History of U.S. Patent No. 10,590,189, Information Disclosure Statement by Applicant, considered by Examiner James L Rogers, May 31, 2019
1033	Esther M. Yoo et al., *Human IgG2 Can Form Covalent Dimers*, 170 J. Immunol. 3134 (2003) ("Yoo 2003")
1034	Excerpt from the File History of U.S. Patent No. 10,590,189, Non-Final Rejection, mailed June 11, 2019
1035	Excerpt from the File History of U.S. Patent No. 10,590,189, Notice of Allowance, mailed Jan. 22, 2020

Exhibit No.	Description of Document
1036	Excerpt from the File History of U.S. Patent No. 10,590,189, Amendment in Response to Non-Final Office Action Under 37 C.F.R. § 1.111, mailed Dec. 11, 2019
1037	Jette Wypych et al., *Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms*, 283 J. Biol. Chem. 16194 (2008) ("Wypych")
1038	Stylianos Bournazos et al., *Fc-optimized* antibodies *elicit CD8 immunity to viral respiratory infection*, 588 Nature 485 (2020) ("Bournazos 2020")
1039	Stylianos Bournazos et al., *Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity*, 124 J. Clinical Investigation 725 (2014) ("Bournazos 2014")
1040	Lucie Baudino et al., *Impact of a Three Amino Acid Deletion in the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions*, 181 J. Immunology 4107 (2008)
1041	Toshiyuki Takai et al., *FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects*, 76 Cell 519 (1994)
1042	Falk Nimmerjahn & Jeffrey V. Ravetch, *Fcγ receptors as regulators of immune responses*, 8 Nat. Rev. Immunol. 34 (2008)
1043	Jeffrey V. Ravetch & Jean-Pierre Kinet, *Fc Receptors*, 9 Annu. Rev. Immunol. 457 (1991)
1044	U.S. Patent Application Publication No. 2005/0271660 A1 issued to Yi Wang (filed May 11, 2005, published Dec. 8, 2005) ("Wang")
1045	Charles A. Janeway, Jr. et al., *Chapter 1: Basis Concepts in Immunology*, and *Chapter 3: Antigen Recognition by B-cell and T-cell Receptors*, Immunobiology: the immune system in health and disease, pp. 1-34, 93-122 (5th ed. 2001)

Exhibit No.	Description of Document
1046	Excerpts from Pei-Show Juo, Ph.D., Concise Dictionary of Biomedicine and Molecular Biology (2nd ed. 2001)
1047	Tina Völkel et al., *Optimized linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies*, 14 Protein Engineering 815 (2001) ("Völkel")
1048	Evelyn D. Lobo et al., *Antibody Pharmacokinetics and Pharmacodynamics*, 93 Journal of Pharmaceutical Sciences 2645 (2004) ("Lobo 2004")
1049	Neil S. Lipman et al., *Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources*, 46 ILAR Journal 258 (2005) ("Lipman 2005")
1050	Benny K.C. Lo, *Chapter 7: Antibody Humanization by CDR Grafting*, Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols, pp. 135-159 (2004) ("Lo 2004")
1051	Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 Nature 323 (1988) ("Riechmann")
1052	Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012) ("Reichert")
1053	Bruce Alberts et al., *Chapter 12: Intracellular Compartments and Protein Sorting*, Molecular Biology of the Cell, pp. 551-98 (1994)
1054	Elisabeth E. Adderson et al., *Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenzae Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations*, 89 J Clin. Invest. 729 (1992)

Exhibit No.	Description of Document
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
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)
1062	Declaration of Cindy Ippoliti, Pharm.D.
1064	Excerpt from The Merck Manual (17th ed. 1999)
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)

Exhibit No.	Description of Document
1066-1100	*Reserved*
1101	Deposition of Arturo Casadevall, dated Jan. 24, 2020
2005	SOLIRIS® Label
2006	Dmytrijuk et al., FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993-1000 (2008)
2007	Janeway and Travers, *Immunobiology:* The Immune System in Health and Disease (Garland Science, 6th ed. (2005))
2008	McCloskey *et al.,* Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
2009	Torres *et al.,* The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
2010	Janda *et al.,* Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22): 1-10 (2016)
2011	Pritsch *et al.,* Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
2012	Pritsch *et al.,* Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)

Exhibit No.	Description of Document
2013	McLean *et al.,* Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
2014	Greenspan et al., Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
2015	Radbruch, *et al.,* Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
2017	Hawkins *et al.,* The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)
2018	Excerpts from Alexion Pharmaceuticals, Inc. Form 10-K for fiscal year ended December 31, 2018
2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)
2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)

Exhibit No.	Description of Document
2022	Declaration of Arturo Casadevall, M.D., Ph.D. submitted in IPR2019-00739, dated Nov. 22, 2019
2023	Curriculum Vitae of Arturo Casadevall
2024	Declaration of Bernhardt L. Trout, Ph.D. submitted in IPR2019-00739, dated Nov. 22, 2019
2025	Curriculum Vitae of Bernhardt L. Trout, Ph.D.
2028	Hill, et al., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007
2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
2030	3/16/2007 FDA Approves Alexion's Soliris™ for all Patients with PNH
2031	Janeway, et al., Immunobiology, The Immune System in Health and Disease, Appendix I: Immunologists' Toolbox, 6th ed., 696-97 (2005)
2033	Kim, et al., Antibody Engineering for the Development of Therapeutic Antibodies, MOLECULES AND CELLS, Vol. 20, No. 1, pp. 17-29, 2005
2034	Hwang, et al., Immunogenicity of engineered antibodies, SCIENCE DIRECT, 17 Jan. 2005
2035	Shepherd, et al., Monoclonal Antibodies, Oxford University Press, pp. 58-5 (Appendix) 2000
2036	Lo, Benny K., Antibody Engineering Methods and Protocols, METHODS IN MOLECULAR BIOLOGY, Vol. 248 2004

Exhibit No.	Description of Document
2037	Welt, et al., Phase I Study of Anticolon Cancer Humanized Antibody A33, CLINICAL CANCER RESEARCH, 2003
2038	Haller, et al., Safety Issues Specific to Clinical Development of Protein Therapeutics, NATURE PUBLISHING GROUP, 2008
2039	Torres, et al., Exchanging Murine and Human Immunoglobulin Constant Chains Affects the Kinetics and Thermodynamics of Antigen Binding and Chimeric Antibody Autoreactivity, PLOS ONE, 2007
2040	Torres, et al., Variable-Region-Identical Antibodies Different in Isotype Demonstrate Differences in Fine Specificity and Idiotype, JOURNAL OF IMMUNOLOGY, 2005
2042	Mathieu, Barbara G., Clinical Testing of Biologically Derived Therapeutics, Biologics Development: A Regulatory Overview, 3d ed., 2004
2043	Andersen, et al., Production technologies for monoclonal antibodies and their fragments, SCIENCE DIRECT, 2004
2044	Chadd, et al., Therapeutic antibody expression technology, 2001
2045	2007 USP Dictionary of USAN and International Drug Names
2046	Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, 1997
2047	McClean, et al., A point mutation in the CH3 domain of human IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
2049	HemOnc Today, Eculizumab's triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)

Exhibit No.	Description of Document
2050	Fatimah Al-Ani et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations, Ther. Clin. Risk Manag., 12:1161-1170 (2016)
2051	Foote, Jefferson and Winter, Greg, "Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops," J. Mol. Biol., 224:487-449 (1992)
2052	Xiang, Jim et al., Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops," J. Mol. Biol. 253:385-390 (1995)
2053	June 2019 Soliris® Label
2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris ™ (eculizumab)," (Sept. 20, 2006)
2055	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris ™ (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," (Sept. 26, 2006)
2075	GenScript, "Final Report- Antibody Full Length Sequencing of Hybridoma 5G1.1 T175," Order Number: U856UEK140-1 (Nov. 15, 2019)
2079	Chang, Byeong S. and Hershenson, Susan, "Practical Approaches to Protein Formulation Development," Pharmaceutical Biotechnology Vol. 13, 1-25 (2002)
2080	Wang, Wei, "Instability, stabilization, and formulation of liquid protein pharmaceuticals," International Journal of Pharmaceutics, 185:129-188 (April 28, 1999)

Exhibit No.	Description of Document
2081	Hermeling, S. et al., "Structure-Immunogenicity Relationships of Therapeutic Proteins," Pharmaceutical Research, 12:6, 897-903 (June 2004)
2082	Frokjaer, Sven and Otzen, Daniel E., "Protein Drug Stability: A Formulation Challenge," Nature Reviews, Drug Discovery, 4:298-306 (April 2005)
2083	Rosenberg, Amy S., "Effects of Protein Aggregates: An Immunologic Perspective," AAPS Journal 8, Article 59, pp. E501-E507 (Aug. 4, 2006)
2084	ICH Topic Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," European Medicines Agency (July 1996)
2085	U.S. Depart of Health and Human Services, FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," ICH Rev. 2 (Nov. 2003)
2086	Stebbings, R., et al., "After TGN1412: Recent developments in cytokine release assays," J. of Immunotoxicology, 10(1): 75-82 (2013)
2088	Amgen Biosimilar Pipeline Approved Products (2019)
2089	Generium Pharmaceutical, "Elizaria" Product (2019)
2090	Samsung Bioepis – Biosimilar candidates and Novel biologic (2019)
2091	Harlow and Lane, Chapter 15: Antibody Molecules, in Antibodies, A Laboratory Manual, 622-25 (1988)
2104	Deposition Transcript of Jeffrey V. Ravetch, M.D., Ph.D. (Feb. 23, 2024)
2105	Declaration of Arturo Casadevall, M.D., Ph.D., 2024

Exhibit No.	Description of Document
2106	Deposition Transcript of Cindy Ippoliti, Pharm.D. (Feb. 20, 2024)
2107	Declaration of Bernhardt L. Trout, Ph.D., 2024
Paper 9	Decision – Institution of *Inter Partes* Review, dated Dec. 8, 2023 ("ID")
Paper 13	Patent Owner's Response Under 37 C.F.R § 42.120, dated Mar. 12, 2024 ("POR")

II. Opinions Responding to Alexion's Response

6. As set forth below, I disagree with arguments made by Patent Owner in their Patent Owner Response, and with the opinions expressed by Drs. Casadevall and Trout which were submitted in a different IPR proceeding involving Amgen that Alexion is relying on here.

A. Alexion Relied on Expert Testimony Recycled from a Different Legal Proceeding

7. Alexion's experts Dr. Casadevall and Dr. Trout submitted short declarations created for this matter, and also submitted the declarations they created for prior Amgen IPRs that pertain to the '504. Specifically, in this matter, I understand that Alexion submitted a short declaration from Dr. Casadevall as Exhibit 2105 (ALXN2105). Similarly, Alexion submitted a short declaration from Dr. Trout as Exhibit 2107 (ALXN2107).

8. These declarations contain only a few pages each, and each refers back to an earlier declaration from a different legal proceeding involving Amgen. For example, Dr. Casadevall's ALXN2105 contains eleven paragraphs in total, and relies on his declaration submitted in the Amgen IPR which was filed in this proceeding as ALXN2022. Similarly, Dr. Trout's ALXN2107 contains nine paragraphs in total, and relies on his declaration submitted in the Amgen IPR which was filed in this proceeding as ALXN2024.

9. In both cases, each expert claims to have reviewed my declaration and that of Samsung's other expert, Dr. Ippoliti. (ALXN2105, ¶6; ALXN2107, ¶6.) Each expert then makes a blanket statement "it is my opinion that the claims of the '504 patent are valid over all of the art and arguments presented by Samsung in its IPR regarding the pharmaceutical compositions recited in the claims of the '504 patent." (ALXN2107, ¶8; *see also* ALXN2105, ¶8.) Each of these experts then states that they disagree with the opinions I expressed in my initial declaration, although neither expert says what the basis for this disagreement is, or otherwise provides any substantive response to the opinions I expressed. I respond to the arguments presented by Alexion in its Response, and opinions presented by Drs. Casadevall and Trout in their declarations from the Amgen IPRs below. I note that although Alexion's Response only cites to specific parts of Dr. Casadevall's and Dr.

Trout's 2019 Amgen declarations, and sometimes seems to do so using erroneous citations, I reviewed the entirety of Dr. Casadevall's and Dr. Trout's declarations and my rebuttals to their opinions are encapsulated in the statements below.

B. Alexion Mischaracterizes the Clear Teachings of Its Own Prior Art and the Import of Its Admissions

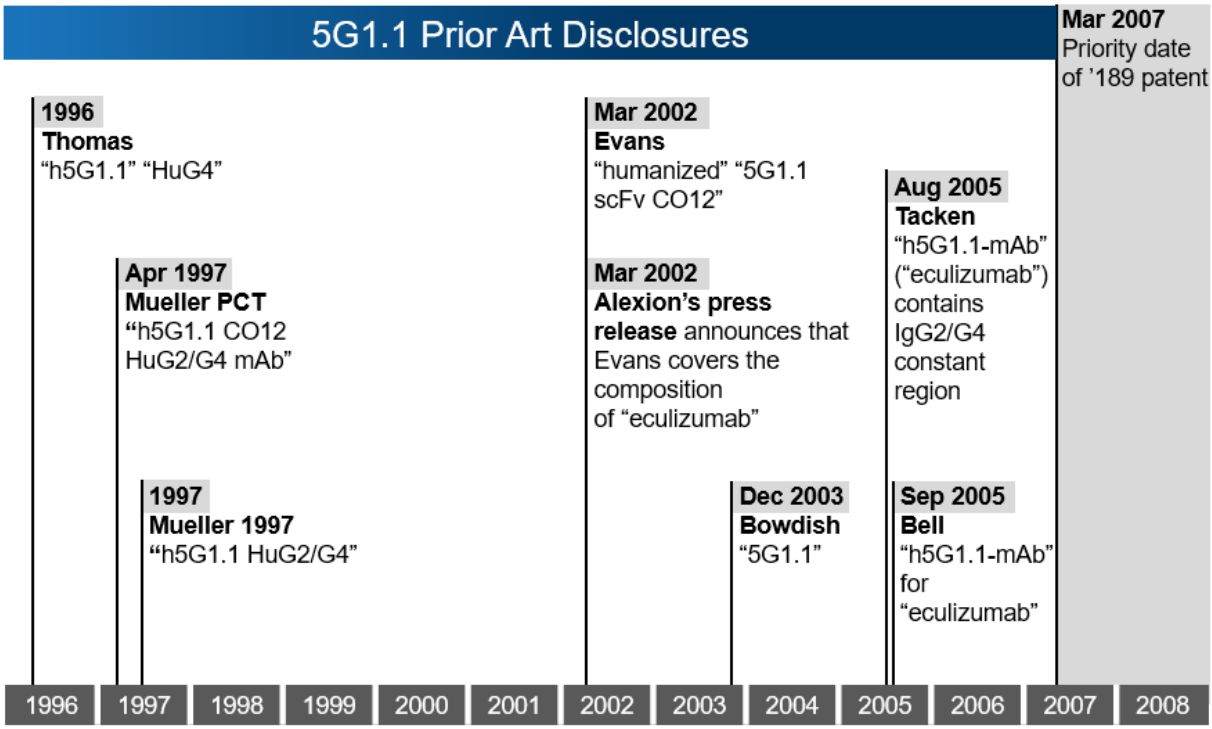
10. Alexion's Response wrongly states that "the literature as of March 15, 2007 consistently identified 'eculizumab' as the antibody described in the 'Thomas' publication[.]" (Alexion Patent Owner's Response (Paper 13) ("POR"), 2.) As I explained in detail in my declaration, and reiterate below, this statement is incorrect, both as a simple factual matter in terms of the written content of the prior art, and especially in terms of how the prior art would be viewed by a POSA.

11. As an initial matter, I note that Thomas does not contain the word "eculizumab" anywhere, and that even Dr. Casadevall agrees with this irrefutable reality. (EX1003, ¶165; EX1010; EX1101, 186:19-22.) On the contrary, the prior art does clearly identify eculizumab's constant domain in the Tacken reference, which is directly associated with Alexion, and which directly states that it is an IgG2/G4 antibody. I explained the teachings of Tacken, and their major significance to a POSA, in my initial declaration. (EX1008, 011; EX1003, ¶¶64, 100, 125, 129.)

12. I disagree with any suggestion that the clear disclosure of the Tacken

reference would have been ignored by a POSA, or that a POSA would have somehow downplayed that disclosure in favor of other, older references. In fact, the prior art showed a linear and direct path beginning with Thomas' early 5G1.1 anti-C5 antibody, which originated as a mouse antibody and was humanized according to standard techniques widely in use by the 1990s. This humanized antibody was then further developed by Alexion into the hybrid IgG2/G4 form expressly disclosed by Tacken and used in Bell.

13. I specifically disagree that a POSA would have been at all confused by the use of the term 5G1.1, or by citations to the Thomas reference, in the literature. As I previously explained in my Declaration, the meaning of 5G1.1, including whether it refers to a mouse or a human antibody, is clear to a POSA from the context in which it appears. (Paper 2, ("Pet."), 9-13; EX1003, ¶¶61-70.) Thus, and as I further explained during my deposition, a POSA understood whether a reference discussed early discovery and humanization of a mouse anti-C5 antibody, or the further development and modification of that antibody into an IgG2/G4 form that was in clinical trials. (*Id.*; ALXN2104, 188:12-192:1.) In my previous declaration I provided a chart of the various disclosures describing the development of the antibody originally called 5G1.1 into eculizumab from 1996 through the March 2007 priority date of the patent.



(EX1003, ¶69.)

14. In my review of Alexion's Response, it appears to me that Alexion is seeking to portray the prior art, even though it comprises Alexion's own publications charting the development of its own eculizumab antibody, as somehow being confusing or misleading to a POSA. (POR, 18, 23-26.) As I have stated, and reiterate further below, there is no such ambiguity in the literature. A POSA would be able to interpret, with confidence, the art's use of terms like "5G1.1," "h5G1.1.," and "eculizumab," in combination with the specific sequence teachings of the prior art, in order to arrive at the sequence of eculizumab.

15. As one example, I note that Alexion seems to place great emphasis on

the fact that Bell cites to Thomas, while also downplaying that Bell also cites Evans, and then argues that a POSA would have simply stopped with Thomas and disregarded the Tacken reference, even though it was published at approximately the same time as Tacken. (POR, 41-42, 53.) In my opinion, this portrayal of how a POSA would interpret the art greatly underestimates the level of skill and intelligence of a POSA in this field.

16. It is entirely appropriate and understandable that later references, including Tacken, cite to Thomas when discussing that eculizumab (or h5G1.1, or 5G1.1) is an anti-C5 antibody. Thomas was the original publication detailing the specific CDR sequences essential for C5 binding as well as the construction of those sequences into various forms of humanized antibodies and antibody fragments. A POSA would not, however, conclude from citation to Thomas that eculizumab is an IgG4 antibody, merely because Thomas includes a disclosure of a full length IgG4 antibody, for one simple reason: There is not one single location in the literature that states that eculizumab is the IgG4 antibody disclosed in Thomas, while there is a clear statement in the literature that eculizumab is an IgG2/G4 antibody. (EX1008, 010-011.) A POSA would not be even slightly confused by the collective teachings of the prior art in context.

17. My views on this are supported by the fact that Alexion has agreed with

me that the level of skill in this art was high, even going so far as to clarify in its briefing that under this agreed definition a POSA would have experience specifically in "engineering monoclonal antibodies for human therapeutic use[.]" (POR, .) So there is no dispute that a POSA in this field was highly skilled and well-informed, indeed specifically experienced with the exact topic of antibody engineering that covers the conversion of an antibody from an IgG4 to an IgG2/G4 form. A POSA (even without Alexion's added level of experience with antibody engineering) would not have focused exclusively on the eleven-year old Thomas reference, and could easily understand the meaning of the various 5G1.1 terms over the course of eculizumab's development from the context in which they appear – as I explained previously and during my deposition in this matter. (EX1003, ¶¶61-70, 112, 130, 151, 165, 182; ALXN2104, 34:6-35:7, 66:5-67:6.) Indeed, I note that Alexion's Response and Dr. Casadevall admit "the precise meaning of the various '5G1.1' terms depends on the context in which it appears[.]" (POR, 10; *see also* ALXN2022, ¶121 ("a POSA would have understood that the terms '5G1.1' or 'h5G1.1' could potentially refer to multiple different antibody structures (when not further limited or clarified by additional context)[.]").) I agree that a POSA would easily have been able to interpret the teaching of the prior art based on that context.

18. I have examined Dr. Casadevall's declaration from the previous Amgen

IPR of the ’504 patent on these points, and I disagree with his opinions. (*See, e.g.*, ALXN2022, ¶¶123-125, 131, 133, 139-151.) In ¶¶123-125 of his declaration, Dr. Casadevall summarizes the teachings of the Thomas reference, and uses quotation marks in a questionable manner when he refers to “Thomas and the following literature regarding ‘eculizumab[.]’” (ALXN2022, ¶125; *see also id.*, ¶123.) I find Dr. Casadevall’s usage of quotation marks to be misleading and inappropriate, to the extent that Dr. Casadevall wishes to create the impression by using quotation marks that Thomas expressly refers to eculizumab. For example, I note that Dr. Casadevall emphasizes in this paragraph that Evans does not contain the word “eculizumab,” while curiously omitting that Thomas does not either – even though he was forced to admit this fact in deposition. (EX1101, 186:19-22.)

19. In ¶131 of his declaration, Dr. Casadevall refers to “the final, IgG4 isotype, as a POSA would have understood from clinical study publications.” I do not understand what Dr. Casadevall is referring to and I note he provides no citation to support his statement. I find the way Dr. Casadevall presents his statements to be questionable and misleading. There is no dispute and Alexion has repeatedly admitted that the eculizumab used in the clinical study publications (e.g., Bell, Hillmen, and Hill) was an IgG2/G4 antibody and <u>not</u> an “IgG4 isotype” as Dr. Casadevall falsely suggests. (EX1007; EX1011; EX1012; EX1003, ¶70.)

20. In ¶133 of his declaration, Dr. Casadevall says "[b]ased on the art as a whole, as of [March 15, 2007], a POSA would have understood 'eculizumab' to be an IgG4 antibody." He is wrong, and in fact the exact opposite is true. As of that date Tacken made clear that eculizumab was not an IgG4 antibody but was instead an IgG2/G4 antibody.

21. In ¶¶139-151 of his declaration, Dr. Casadevall attempts to downplay or otherwise explain away the Tacken reference's clear disclosure. A POSA would not have understood the prior art in the cramped, myopic manner in which Dr. Casadevall does. For example, he refers to Tacken as "ambiguous," but it is not ambiguous at all. Tacken states, in plain English, that the authors tested "h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region[.]" (EX1008, 011; EX1003, ¶100.) As I previously explained, "the same" in Tacken refers back to Alexion's own Mueller reference (EX1006) – which is just more confirmation that eculizumab is an IgG2/G4 antibody. (EX1003, ¶100.) Dr. Casadevall's misreading of Tacken's citation to Mueller 1997 (ALXN2022, ¶148) is thus wrong. Dr. Casadevall also argues that Tacken's citation to Thomas would have been read by a POSA describing "an IgG4 isotype antibody that the other prior art consistently identified as 'eculizumab[.]'" (ALXN2022, ¶144.) Dr. Casadevall's argument is thus circular, because it is based

on his false premise that other prior art "identified" eculizumab as an IgG4 antibody, when in fact there is not one piece of prior art which states that eculizumab is an IgG4 antibody. Dr. Casadevall's other opinions seeking to downplay Tacken are also wrong. (ALXN2022, ¶¶145-151.) For example, Dr. Casadevall criticizes Tacken for not itself containing safety or efficacy data, which is irrelevant to this issue, and even conjectures implausibly that a POSA would have thought Tacken's disclosure that eculizumab is an IgG2/G4 antibody was "a mistake" (ALXN2022, ¶147) – even though one of Tacken's authors was a named inventor on the challenged patent. Simply put, a POSA would not read the prior art in the way that Dr. Casadevall has chosen to read it. Instead, a POSA would accept the prior art for all it teaches, in context, which includes the unsurprising disclosure that Alexion further developed the original IgG4 antibody of Thomas into the IgG2/G4 type disclosed by Tacken with direct reference to eculizumab – particularly unsurprising given Alexion's well-published interest in and development of antibodies with an IgG2/G4 constant domain. (EX1003, ¶62; EX1006; EX1009.)

C. Ground 1: Claims 1-5 and 7-10 Are Obvious over Bell, Bowdish, and Evans in View of Tacken and Mueller PCT

1. No Dispute that the Prior Art Taught Eculizumab Was an Effective PNH Treatment; No Dispute that the Prior Art Sequences Read on the Challenged Claims

22. Alexion's Response does not dispute that Bell teaches eculizumab as an effective treatment for PNH and does not dispute that the sequence disclosed in the Bowdish/Evans integrated document expressly discloses the claimed sequences, with a perfect match as shown in alignments.

23. Alexion also raises no disputes relating to any of the specific limitations found in challenged claims 2-5 and 7-10.

24. The only dispute remaining is motivation and reasonable expectation of success, and as discussed below Samsung has met its burden to show obviousness in view of those factors.

2. A POSA Would Have Followed Samsung's Obviousness Rationale

25. I note at the outset that Alexion does not seem to offer any dispute that Bell teaches eculizumab as a treatment for PNH, or that a POSA would have been motivated to prepare eculizumab based on the teachings of Bell (and other clinical trial literature like it). (EX1003, ¶111.) I note that Alexion also does not seem to offer any dispute that the combined teachings of the integrated Bowdish/Evans

disclosure do, in fact, provide a 100% match to the sequence of eculizumab that is recited in the challenged claims as SEQ ID NOS:2 and 4. (EX1003, ¶¶113-116.) Finally, I note that there is nothing in Alexion's Response that disputes my obviousness opinions specifically with respect to challenged claims 2-5 and 7-10. (EX1003, ¶¶134-143.) Indeed, as I have noted, Alexion's experts offered no substantive expert testimony at all in rebuttal to my opinions regarding the '504 patent, and in this matter they have merely referred back to the prior declarations from the Amgen IPR, which do not rebut my opinions submitted in this case in support of Samsung's Petition. (*See* ALXN2022, ¶¶192-234.)

26. The obviousness route I proposed in my previous declaration was one that a POSA would have followed. As I explained above, I do not agree with the view of the prior art in which a POSA would note repeated citation to the Thomas reference and simply end their inquiry there. To restate my original opinion: Start with Bell's teaching that eculizumab (which it calls "the antibody h5G1.1" and "h5G1.1-mAb") is an effective treatment for PNH. From there, a POSA would have been led first to Evans and Thomas, both of which are cited and incorporated by Bell for "methods of preparation" of h5G1.1. (EX1007, [0012], [0052], [0082]; EX1003, ¶¶111-112, 132.)

27. As I have previously explained, a POSA would also have recognized

with no difficulty that Evans provides variable region sequences for eculizumab. A POSA would also easily have seen that Thomas' full-length IgG4 antibody could not be correct for eculizumab, because a POSA knew from the clear teaching of Tacken that eculizumab has an IgG2/G4 domain. (Pet., 29-30, EX1003, ¶112.)

28. A POSA would not simply stop there as Alexion and Dr. Casadevall contend. A POSA was motivated, and highly skilled, and thus would have kept searching for relevant literature of the 5G1.1 antibody discussed by Bell and Evans. In so doing, a POSA would have found Bowdish particularly relevant. Bowdish provides express disclosures about the structure of an antibody it calls "5G1.1," Bowdish also identifies "Alexion Pharmaceuticals" as the inventors' addressee, and Bowdish also cites to and incorporates the same Evans patent as does Bell for the structure of 5G1.1. (EX1004, Cover, [0191]; EX1003, ¶122.) I thus disagree with Alexion's argument that Bowdish is not analogous art. (POR, 43.) On the contrary, Bowdish and its incorporated reference Evans are analogous art for a POSA motivated by Bell to make eculizumab. I explained in my original declaration the standard for analogous art, which Bowdish meets for the reasons I noted in my previous declaration and reiterate in this paragraph. (EX1003, ¶¶28, 122.)

29. I similarly disagree with Alexion's argument that Thomas' IgG4 disclosure is a teaching away from the IgG2/G4 teachings of Tacken and the

expectations of a POSA. (POR, 46.) I understand that a reference teaches away if it criticizes, discredits, or otherwise discourages investigation into what is claimed as an invention. The prior art does not meet this standard, at least because Tacken expressly disclosed that eculizumab was an IgG2/G4, and no reference anywhere actually offers any negative statement that would criticize or discourage research into an IgG2/G4 format for an anti-C5 antibody. At most, Thomas discloses the existence of an IgG4 format of an anti-C5 antibody (although it never uses the term eculizumab), but this does nothing to teach away from the use of other subclasses of IgG antibody structures – especially given the teachings of Tacken, Mueller PCT and Mueller 1997. (*See* EX1003, ¶¶62, 64.)

30. A POSA would have been further motivated to rely on Bowdish and Evans because they would have easily been able to tell that the heavy chain sequences disclosed in Bowdish's SEQ ID NO: 67 were of a human hybrid subclass. This is the subclass Tacken taught would be expected for eculizumab, and as I previously explained, a POSA could have easily confirmed this by aligning the constant domain sequences taught in the combined Bowdish/Evans disclosure with the sequences of Mueller PCT. Such routine alignment would instantly confirm that the antibody under consideration was indeed the IgG2/G4 type as desired. (EX1003, ¶¶125-128; ALXN2104, 150:13-152:24.)

31. Alexion suggests a POSA would have been confused in reading Bowdish as to whether it dealt with human or mouse sequences, because it uses the term "5G1.1" instead of "h5G1.1." I disagree, because a POSA would know that eculizumab was a humanized antibody and would have easily recognized that Bowdish discloses humanized rather than mouse sequences. Reasons for this include the fact that Evans expressly discloses that its framework regions (which align perfectly with Bowdish's) are human, as well as Bowdish's use of an anti-human IgG for its binding assay to detect the antibody it refers to as 5G1.1. (EX1003, ¶83, 123-124; ALXN2104, 142:17-145:6.)

32. I note that Alexion accuses me of violating the rule against using "hindsight," and says I worked backwards from the claimed sequences. Alexion seems to criticize the fact that my previous declaration included alignments that showed how the combined antibody sequences of the prior art align perfectly with the claimed sequences. (POR, 47.) I did not use hindsight in my analysis, nor did I work "backwards" from the claimed sequences. As I explained in my original declaration, I understand the need to guard against hindsight, and I did so by beginning with the motivation from Bell to make the anti-C5 antibody eculizumab and the clear knowledge from Tacken that eculizumab had an IgG2/G4 constant domain. With that foundation, I sought to identify in the prior art sequences that

would be considered by a POSA to be eculizumab, in light of the art's clear guidance. (EX1003, ¶¶24, 111-132; ALXN2104, 55:19-56:12, 93:7-21, 155:9-156:3.) I included sequence comparisons against SEQ ID NOS:2 and 4, because I understand that part of obviousness requires me to show differences (if any) between the teachings of the prior art and what is recited in the claims. (EX1003, ¶¶114-116.)

33. I have examined Dr. Casadevall's declaration from the previous Amgen IPR of the '504 patent on the points discussed in this section, and I disagree with his opinions as explained further below. (*See, e.g.*, ALXN2022, ¶¶192-234.)

34. I disagree with Dr. Casadevall's opinions of how a POSA would have interpreted the teachings of Bowdish and Evans. As an initial matter, as I noted in my original declaration, U.S. Application Ser. No. 08/487,283, which issued as the Evans patent, was incorporated by reference into Bowdish for "Construction of 5G1.1." (EX1003, ¶¶82, 89, 113, 121.) I have not seen any argument that there is any significance to the fact that Bowdish references the Evans disclosure in the format of an application serial number as opposed to using the format of Evans as an issued U.S. patent, and Dr. Casadevall does not identify any differences in the disclosure or any reason this distinction would matter. (ALXN2022, ¶212, n.10.)

35. First, I disagree that a POSA would have thought Bowdish was incorporating Evans for disclosures of only mouse antibody sequences.

(ALXN2022, ¶¶203-208, 213-216.) Dr. Casadevall's opinions here all seem to hinge on the fact that Bowdish uses the term "5G1.1" without preceding it with an "h," but as I explained in my original declaration and at length above, a POSA would know from context (and the disclosures of the references) that Bowdish, like Evans, contained disclosures of human antibody sequences for 5G1.1. Dr. Casadevall also generally discusses the development of antibodies beginning with mouse polyclonal antibodies to humanized monoclonal antibodies, and the fact that mouse antibodies are generally disfavored as candidates for use as pharmaceutical compositions for use in human patients. (ALXN2022, ¶¶70-76.) While this general discussion may be correct, it does not apply to my opinions regarding the obviousness of the challenged claims, given that the prior art in this case contained extensive teachings about eculizumab, including that it was a humanized anti-C5 antibody with a hybrid IgG2/G4 constant domain.

36. Second, I disagree that a POSA would have been "lost" or unable to combine the teachings of Evans with Bowdish. (ALXN2022, ¶¶200-202, 214, 217-219.) Actually, and as I explained in detail, there was an easy, obvious path to obtain the full sequence of humanized 5G1.1 (which the prior art taught was eculizumab) by removing the inserted TPO peptide and swapping back in the original HCDR3 taught in Evans. (EX1003, ¶¶82-86, 113-117, 128.)

37. Third, I disagree that there would have been any confusion from the multiple scFv sequences disclosed in Evans. (ALXN2022, ¶220.) On the contrary, and as I explained in my previous declaration, there is apparently no dispute that Evans consistently teaches only one single HCDR3 sequence in the context of the scFv sequences which it expressly states could be used to make full length antibodies. (EX1003, ¶¶89-91, 117-120, 128, 133, Appendix A.) Dr. Casadevall's remaining opinions in this area appear to be rebuttals of a different expert (Dr. Balthasar) in the different Amgen IPRs, and thus it is not apparent that these are pertinent or responsive to the opinions expressed in my previous declaration; to the extent they contain relevant arguments I address them herein. (ALXN2022, ¶¶205-206, 221-224.) I address reasonable expectation of success next.

3. A POSA Would Have Had a Reasonable Expectation of Success

38. As I explained in my previous declaration, a POSA would have had a reasonable expectation of success that the sequences provided by the prior art would possess the known anti-C5 properties of eculizumab. (EX1003, ¶¶132-133.) I thus disagree with the concerns of unpredictability raised in Alexion's Response. (POR, 46.) As an initial matter, a POSA already knew that eculizumab had an IgG2/G4 constant region, thus a POSA would not have any concern that they were testing a

different antibody from what had already been successfully tested as a PNH therapy as shown in Bell and other clinical trial references. (EX1003, ¶¶112, 125, 127-128,, 132-133.)

39. As I previously explained, antibodies with an IgG2/G4 constant region were known in the art by 2007. (EX1003, ¶¶48, 62; EX1006, 011, 013, 015-016; EX1009, 014, 097; EX1021, 011, 019, 028.)

40. Second, as also previously explained, Mueller and other references taught that a hybrid constant region made of G2 and G4 subclass components was desirable for reduced activation of the complement system. (EX1003, ¶48; EX1006, 011, 013, 015-016; EX1009, 014, 097.)

41. Third, as also previously explained, Evans expressly encouraged a POSA to construct complete 5G1.1 antibodies with different constant regions, including constant regions made of hybrids of different antibody classes. (EX1005, 45:29-33; EX1003, ¶157.) I therefore disagree with any suggestion that Evans discloses only parts or fragments of antibodies, because Evans expressly encourages (and a POSA would know how) to construct full length antibodies following the teachings of Evans.

42. I have also examined Dr. Casadevall's declaration from the Amgen IPR relating to the '504 as it relates to these issues. I disagree with Dr. Casadevall's

concerns regarding potential loss of C5 binding activity caused by what he considers to be changes to the constant region as between IgG4 and IgG2/G4. (ALXN2022, ¶¶105-118, 226-234.) I note at the outset that Dr. Casadevall acknowledged in deposition that none of the examples he relies on to support this supposed concern involved an IgG2/G4 antibody. (EX1101, 191:7-12, 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18.) Dr. Casadevall also makes a passing reference to potential issues with efficient cellular expression of an IgG2/G4 antibody (ALXN2022, ¶117), but cites a single example involving a different antibody, and nothing in the prior art including Bell or Tacken ever suggested that there were any expression issues with eculizumab. And there was no reason to expect them, as such issues only occur rarely. Indeed, Alexion's choice to develop eculizumab as a "potential product," which Tacken again taught was an IgG2/G4, would dispel any such concerns with the efficiency of protein production. (EX1008, 010; EX1003, ¶100.)

43. I address each of Dr. Casadevall's specific examples from the literature, which he incorrectly attempts to generalize, in the following paragraphs. As I explain below, a POSA would have been aware of each of the specific examples Dr. Casadevall refers to, and would not have less of a reasonable expectation of success from any of these examples (none of which involve an anti-C5 or an IgG2/G4

antibody).

44. Dr. Casadevall points to "changes to 'framework' amino acids within the variable regions, but outside the CDRs," citing ALXN2051 (Foote 1992) and ALXN2052 (Xiang 1995). (ALXN2022, ¶107.) These references would not have undermined a POSA's reasonable expectation of success because changes to the framework region affecting CDR binding to an antigen are unique to the variable domain and do not implicate changes to the constant region. As I explained in my original declaration, the framework residues provide a scaffold on which the CDRs are able to access the antigenic epitope. (EX1003, ¶38.) The changes to the framework region described in this reference are in an entirely different region of the antibody than the constant region, and thus a POSA's reasonable expectation of success would not be diminished by them.

45. Dr. Casadevall cites to ALXN2035 (Shepherd 2000). (ALXN2022, ¶107.) This reference would not have undermined a POSA's reasonable expectation of success because Shepard provides a standard protocol for variable region humanization by CDR grafting. As discussed above, changes to the framework region that may impact on CDR binding to an antigenic epitope are unique to the variable domain, and a POSA would not have been concerned by this reference in the context of the IgG2/G4 hybrid constant domain of eculizumab.

46. Dr. Casadevall cites to ALXN2036 (Lo 2004). (ALXN2022, ¶107.) This reference would not have undermined a POSA's reasonable expectation of success because, similar to the Shepard reference, Lo deals with CDR grafting and the impact of framework substitutions on CDR binding affinity. It does not suggest that changes to the constant domain would have any impact on variable region binding.

47. Dr. Casadevall opines that "a POSA would have understood that 'isotype switching' – changing an antibody's constant region sequences while retaining sequences from the variable region – could impact critical properties such as an antibody's specificity and affinity, as well as other properties such as immunogenicity," citing to ALXN2013 (McLean 2002). (ALXN2022, ¶¶108-109.) However, this reference would not have undermined a POSA's reasonable expectation of success because McLean is concerned with antibodies binding to polysaccharide antigens and not protein antigens, and describes results based on immunofluorescence patterns. Indeed, the authors of the reference (which includes Dr. Casadevall) recognized that the observed differences for different isotypes with the same variable region was attributed to the repetitive nature of the polysaccharide antigen. (*See* ALXN2013, 1379 ("This phenomenon may be most apparent for Abs that bind to Ag with repeating epitopes, such as polysaccharides, where the

quarternary structure of the Ag-Ab complex may be influenced by such constraints as Fab-Fab angles, Fc-Fc interactions, Ab size, and solvent accessibility to exposed surfaces.”).) Because of these differences, ALXN2013 would not be of concern to a POSA dealing with anti-C5 antibodies. As I discuss below, the same is true for the rest of the references Dr. Casadevall cites as supposedly supporting his point that changes to the constant domain can impact antigen binding. Instead, the phenomenon for repeating/polysaccharide-type antigens under study in Dr. Casadevall’s laboratory would have been understood by a POSA as of 2007 as a somewhat unique phenomenon for a specific class of antigens – not a generalizable fact about antibodies overall.

48. Dr. Casadevall points to other work from his own laboratory, citing ALXN2013 (McLean 2002), ALXN2040 (Torres 2005), and ALXN2009 (Torres 2007). (ALXN2022, ¶108.) These references would not have undermined a POSA’s reasonable expectation of success because Torres, similarly to McLean, deals with murine anti-polysaccharide switch variants. In addition to the reasoning set forth above, these three exhibits are also different because they point mainly to differences between mouse and human isotypes. Thus, they would not diminish the expectation of success by a POSA in developing an IgG2/G4 constant region for an anti-C5 antibody. Indeed as noted throughout my declarations, Tacken explicitly

points to the IgG2/G4 hybrid constant region for the anti-C5 antibody h5G1.1 called eculizumab, and Bell provides data showing eculizumab is an effective PNH treatment, confirming that the IgG2/G4 constant region did not disturb the ability of the antibody to recognize its C5 antigen.

49. Dr. Casadevall also points to a review article he co-wrote, ALXN2010 (Janda 2016). (ALXN2022, ¶¶108, 115.) First, I note that the Janda reference is a review article that covers at a high level the same kinds of original research reports that are discussed by Dr. Casadevall, and thus I deal with those studies in other paragraphs in this section of my declaration. As a result, this reference would not have undermined a POSA's reasonable expectation of success because it again deals with the observations cited above regarding antibodies with specificity for repetitive epitopes and would not diminish the expectation of success for an POSA developing an anti-C5 antibody with a hybrid IgG2/G4 constant domain.

50. Dr. Casadevall also points to ALXN2014 (Greenspan 1995). (ALXN2022, ¶110.) This reference would not have undermined a POSA's reasonable expectation of success because, like the literature cited above, is primarily concerned with murine switch variants and variable domains with specificity for multivalent targets, such as polysaccharides.

51. Dr. Casadevall also points to ALXN2011 (Pritsch 1996). (ALXN2022,

¶111.) This reference would not have undermined a POSA's reasonable expectation of success because Pritsch reports the results of anti-tubulin antibodies with the same variable domains but which differ in their isotypes (IgA and IgG) display differences in binding affinity. This study thus does not concern a subclass change, such as from IgG4 to IgG2/G4, but rather a switch to an entirely different isotype. A POSA would not consider this study to impact the expectation of success in generating an anti-C5 antibody with a hybrid G2/G4 constant domain because the isotype (IgG) is the same and especially given the teachings of Tacken and Bell as noted above.

52. Dr. Casadevall also points to ALXN2008 (McCloskey 1996). (ALXN2022, ¶112.) This reference would not have undermined a POSA's reasonable expectation of success because McCloskey reports results for chimeric mouse-human IgGs to a mucin-like glycoprotein, which again is a repetitive protein that is heavily decorated with polysaccharides. The C5 target of eculizumab is not a mucin-like glycoprotein, and thus these results would not influence the expectation of success of a POSA developing humanized anti-C5 antibodies with hybrid G2/G4 constant region domains for the reasons cited above.

53. Dr. Casadevall points to three further articles from his laboratory, ALXN2040 (Torres 2005), ALXN2009 (Torres 2007), and ALXN2039 (Torres 2007 PLOS One). (ALXN2022, ¶113 (the first two of these were already referenced

in ¶107 of Dr. Casadevall's declaration).) ALXN2039 would not have undermined a POSA's reasonable expectation of success because, once again, the target polysaccharide multivalent antigen is distinct from the C5 target and none of the studies address the relationship between G4 constant region and G2/G4 hybrid constant region with relation to binding specificity. In contrast, as noted throughout my declarations, Tacken explicitly points to the IgG2/G4 hybrid constant region for the anti-C5 antibody h5G1.1 called eculizumab, and Bell provides data showing eculizumab is an effective PNH treatment, confirming that the IgG2/G4 constant region did not disturb the ability of the antibody to recognize its C5 antigen.

54. Dr. Casadevall states that "a POSA would have been aware of publications describing how changes to the 'CH1' and 'hinge' portions of the heavy chain constant region could impact antibody binding, suggesting that these regions in particular modulated the antibody-antigen interaction," citing ALXN2012 (Pritsch 2000) and ALXN2009 (Torres 2007). (ALXN2022, ¶114.) I disagree. These references would not have undermined a POSA's reasonable expectation of success because, as discussed above, each of these examples dealt with either entirely different isotypes (IgA and IgG) or multi-valent antigens such as polysaccharides, and would not influence a POSA developing an anti-C5 antibody with a hybrid G2/G4 constant region.

55. As I noted above, Dr. Casadevall's examples are drawn from a limited class of antibodies that interact with repetitive carbohydrate epitopes. However, and as I explained in my deposition in this matter, the relevant literature actually indicated that "switching the constant region domain of the heavy chain or light chain has not impacted on the binding specificity or affinity of the original Fab domains." (ALXN2104, 60:13-61:22.)

56. I also discuss further below why both Thomas and Mueller's teachings further show that a POSA would not expect a subclass switch from IgG4 to IgG2/G4 in the context of the 5G1.1 antibody to impact C5 binding ability of the antibody. I noted as much during my deposition in this matter. (ALXN2104, 57:21-58:8 ("we knew quite a bit more about eculizumab than this generic discussion that Dr. Casadevall is presenting.").) (*See* Part II.D.2 below.)

57. Dr. Casadevall also argues that a hybrid IgG2/G4 domain would present heightened immunogenicity concerns, citing ALXN2015 (Radbruch 1985), ALXN2036 (Lo 2004), and ALXN2038 (Haller 2008). (ALXN2022, ¶¶116, 118.) These references would not have undermined a POSA's reasonable expectation of success because these studies deal with modifications to variable domains that may influence antigenic specificity and not to constant region modifications of highly homologous subclasses. Further, a POSA would not have had immunogenicity

concerns in creating eculizumab as an IgG2/G4 antibody working from the prior art as I outlined above, because the art had already confirmed that eculizumab (disclosed by Tacken as a humanized IgG2/G4 antibody) did not trigger an immunogenic response in human patients. (EX1003, ¶¶48, 58; EX1013, 013.)

D. Ground 3: Claims 1-5 and 7-10 Are Obvious over Bell, Evans, and Mueller PCT in View of Tacken

58. To begin, I note that as with Ground 1, there seems to be no dispute that Bell taught a POSA that eculizumab was a useful treatment for PNH, or that the amino acid sequences in the combined disclosures of Evans and Mueller PCT read exactly on SEQ ID NOS:2 and 4 of the challenged claims. (EX1003, ¶156.) I also note, as with Ground 1, Alexion raises no disputes relating to any of the specific limitations found in challenged claims 2-5 or 7-10. I address Dr. Casadevall's arguments relating to the Evans and Mueller PCT combination below. (*See* ALXN2022, ¶¶235-262.)

1. A POSA Would Have Followed Samsung's Obviousness Rationale

59. As I explained in my previous declaration, a POSA working from Bell would have looked to Evans and Mueller PCT, and would have combined them to obtain the desired sequence of the eculizumab antibody. At the first step, Bell points

directly to Evans and Thomas for the amino acid sequence of the anti-C5 antibody eculizumab and incorporates both by reference. (EX1003, ¶¶151-153.) A POSA would not, however, have concluded that eculizumab was an IgG4 antibody from this reference to Thomas, because of the teachings of Tacken and Mueller PCT (which were published after Thomas). (*Id*; *see also* Part II.B above.) Further, a POSA would have known how to combine Evans and Mueller PCT, because a POSA would have been able to differentiate the disclosures of those references as they pertain to variable and constant regions. Thus, a POSA would have used Evans for the C5-binding variable regions of eculizumab, as directed by Bell, and would have used Mueller PCT for the IgG2/G4 constant domains, as directed by Tacken and taught by Mueller PCT. (Pet., 52-56; EX1003, ¶¶153-156.)

60. Further, even if a POSA was somehow unaware of Tacken's IgG2/G4 disclosure, the prior art still contained ample motivation and reasonable expectation of success to modify the constant region of the original IgG4 antibody of Thomas. For example, Evans provides instructions for how to combine 5G1.1 variable regions with constant region domains to form a full-length antibody, and this same part of Evans expressly states that it is "[p]articularly preferred" to use "a mixture of constant domains from IgGs of various subtypes." A POSA would read this to include the IgG2/IgG4 disclosure of Tacken and Mueller PCT. (EX1005, 45:29-33;

EX1003, ¶157.)

61. I understand that Alexion argues that I never identified any reason a POSA would have been motivated to move from an IgG4 to an IgG2/G4 antibody so as to avoid binding Fc receptors. (POR, 42.) This is not true. In fact, as I described in my previous declaration, the Mueller 1997 reference associated with Mueller PCT provides general motivation to convert IgG4 isotype antibodies to the "HuG2/G4 antibody design" in any human antibody intended for therapeutic use "where elimination of FcR binding and C activation may be desirable." (EX1006, 016; EX1003, ¶¶47-48, 158.) Again, as I have previously explained, and explained further in my deposition, a POSA would have recognized these teachings as beneficial in the context of a therapeutic antibody intended for use to block part of the complement system. (EX1003, ¶158; ALXN2104, 169:5-18, 171:12-173:7.)

62. Further, my previous declaration did provide a detailed explanation of why a POSA would have combined Evans and Mueller PCT. (EX1003, ¶¶151-156.) I do not agree that a POSA would have had to apply any guesswork about which amino acids from Evans and Mueller PCT would be used, as Alexion argues. (POR, 17.) Instead, the combination was actually a very simple one involving whole, distinct large regions of the antibodies: Mueller PCT (which a POSA could have confirmed against the teachings of the related Mueller 1997 reference) clearly

showed exactly how to construct an IgG2/G4 hybrid, by combining the C1 region and hinge of IgG2 with the C2 and C3 regions of IgG4. (EX1009, 8:23-26, 12:23-27; EX1006, 011, 013; EX1003, ¶¶48, 103.)

63. As I previously explained, and show with an excerpt below, the Tacken reference gives very clear direction. It explains that eculizumab contains an IgG2/IgG4 constant region, and says it is "the same" as that disclosed in Tacken's reference 17, which is the Mueller 1997 article. Thus, contrary to the implications raised in Alexion's arguments, Tacken does not leave any doubt about what is being disclosed concerning the constant domains used in eculizumab. Tacken provides more than ample disclosure to lead a POSA to Mueller PCT for the needed constant domain sequences. (EX1003, ¶¶100, 157-158.)

> **Recombinant antibodies**
>
> The humanized antihuman DC-SIGN antibody hD1V1G2/G4 (hD1) was generated by complementarity determining region (CDR) grafting of AZN-D1 hypervariable domains into human framework regions. The humanized variable heavy and variable light regions were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively. This construct was cloned into a mammalian expression vector and the final construct transfected into NSO cells. Stable transfectants were obtained using glutamate synthetase (GS) selection (Lonza Biologics, Portsmouth, NH). Supernatants containing hD1 were purified over a protein A column. An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(EX1008, 011 (citing EX1006) (highlighting added).)

64. I note that Alexion also argues that a POSA would not have been able

to differentiate between Evans' multiple variable structures relating to 5G1.1 and instead would have focused on the separately-disclosed mouse antibody, even though a POSA would know from Bell that eculizumab is a humanized antibody. (POR, 52-53.) I disagree and note again that Alexion is not crediting the abilities of a POSA in this field, which is admittedly-highly skilled. Nevertheless, the Evans prior art gave a direct path to a POSA as to how to interpret and use its disclosures. Specifically, Evans' Example 11, entitled "Construction and Expression of Recombinant mAbs," provides a finite set of clearly-identified CDRs that bind C5. (EX1005, Cover (Title), 7:60-64, 9:44-45, 42:56-45:33, 143:22-144:14, Fig. 8, Claim 19 (emphasis added); *see also* EX1022, 16:10-12.) This would have been clear guidance to a POSA – especially since the Mueller PCT disclosure specifically highlights the "CO12" sequence as the only one investigated in that reference. (EX1003, ¶¶152-155.)

65. I note that Alexion again complains that I used hindsight in my Ground 3 analysis. (POR, 55.) Again, I disagree. I began with motivation from Bell and knowledge from Tacken, combined the teachings of Evans and Mueller PCT, and only then did I perform a confirmatory alignment. (EX1003, ¶156 ("[t]he resulting antibody, as shown in the comparisons below, shows a perfect match [with] … the claimed SEQ ID NOS:2 and 4" (emphasis added)).

66. I have examined Dr. Casadevall's declaration from the previous Amgen IPR of the '504 patent on the Evans/Mueller PCT combination as discussed in this section, and I disagree with his opinions as explained further below. (*See, e.g.*, ALXN2022, ¶¶239-254.)

67. In ¶¶239-241 of his declaration, Dr. Casadevall expresses his view that a POSA would not have been motivated to combine Evans with Mueller PCT. I disagree for the reasons articulated above in this section, and in my previous declaration. (EX1003, ¶¶151-153.)

68. In ¶242 of his declaration, Dr. Casadevall argues that a POSA would not have been motivated to construct an IgG2/G4 antibody because that process would supposedly have been complex, time-consuming, and unpredictable. I disagree, for the reasons already noted above (¶59) and in my previous declaration. A POSA would have known from reading Bell and Tacken that eculizumab was an IgG2/G4 antibody that had been successfully used in humans as a PNH treatment. There was thus nothing "new" about making an IgG2/G4 antibody, since Alexion had already published that they had done so. These facts would have removed any complexity or uncertainty from the proposition and made it simple for a POSA to follow the teachings of the prior art (Evans and Mueller PCT) to construct the eculizumab antibody. (EX1003, ¶¶151-156.)

69. In ¶243 of his declaration, Dr. Casadevall makes the curious argument that a POSA, even if motivated to make an IgG2/G4 antibody, would not have known which parts of IgG2 and which parts of IgG4 to use, and might have selected various ways to hybridize those two subclasses. This argument is nonsensical – the prior art Mueller PCT and Mueller 1997 references, both of which are directly associated with Alexion, gave very clear guidance about how to construct the IgG2/G4 hybrid that Tacken expressly says is "the same" as between Mueller 1997 and eculizumab. (*See* ¶63 above and EX1003, ¶¶100, 157-158.) A POSA would not have had any doubt about how to build the constant region, and would not have had any need to creatively try other approaches before simply following the teachings of the Mueller references.

70. In ¶244 of his declaration, Dr. Casadevall again argues that Evans does not teach full length antibodies, but as I have already explained, he is incorrect since Evans does expressly teach how to make full length antibodies using its disclosures, and in any event a POSA could easily have used Evans' scFv sequences relating to variable domains in the assembly of a full-length antibody according to known and conventional techniques. (*See above* ¶37; EX1005, 45:29-33; EX1003, ¶157.) For the same reason, I disagree with the suggestion in Dr. Casadevall's report that the Evans' scFv disclosures were not disclosures of variable domain sequences because

they were recombinant. As I show in my previous declaration, this is wrong because the 5G1.1 C5-binding scFv fragments disclosed in Evans did provide entire variable regions, and a POSA would know how to use those sequence teachings to assemble a full-length antibody. (EX1003, ¶¶89-91, 155-156.)

71. In ¶245 of his declaration, Dr. Casadevall argues that a POSA would not have known how to interpret the term 5G1.1 as it appears in the different prior art references, but he is incorrect for the reasons I discussed in detail above in Part II.B.

72. In ¶¶246-248 and 252 of his declaration, Dr. Casadevall contends that the CO12 disclosure in Mueller PCT would have been disregarded by a POSA and contends that a POSA would not have known how to combine the Evans and Mueller PCT teachings, but he is incorrect as I explained in my original declaration. (EX1003, ¶¶155-156.) As I explained in my previous declaration, even though it would have been simple and routine for a POSA to try Evans' nine sequences, Mueller PCT provides some additional guidance to a POSA specifically to prioritize the construct disclosed in Example 11 (12) that is identified as "humanized" "5G1.1 scFv CO12." Mueller PCT also uses the same identifier, and the only 5G1.1 with the hybrid IgG2/G4 discussed in Mueller PCT is referred to as "h5G1.1 CO12 HuG2/G4." (EX1009, 014.) Mueller PCT does not refer by name to any of the other

constructs provided in Evans' Example 11. Therefore, a POSA would have been motivated to assemble a full-length antibody with Mueller PCT's IgG2/G4 region and constant light chain region, along with Evans' variable regions that use the same identifier, CO12. (EX1003, ¶¶155-156.)

73. In ¶¶249-250 of his declaration, Dr. Casadevall makes references to specific statements by Amgen's expert Dr. Balthasar which are not relevant to my declaration or my testimony. In my previous declaration, I explained how a POSA would have been able to use Mueller PCT (including by confirmation with Mueller 1997) references to easily determine the pertinent regions and subclasses of the disclosed heavy chains. (EX1003, ¶126.) I also explained how a POSA would easily have known how to recognize the distinct regions of an IgG heavy chain of different subclasses. (EX1003, ¶128.)

74. In ¶251 of his declaration, Dr. Casadevall questions why a POSA would not have taken variable regions of 5G1.1 from the Thomas reference as opposed to Evans, and then notes that Thomas' disclosure difference at one amino acid position would not match with the sequence recited in the challenged claims. I do not understand why this argument is pertinent to my obviousness analysis, because as I understand, the prior art can render more than one combination obvious. (*See, e.g.*, EX1003, ¶154.) Evans clearly discloses C5 binding antibody variable domains, so

it doesn't matter if Thomas does as well, especially since Bell cites to both Evans and Thomas.

75. In ¶253 of his declaration, Dr. Casadevall again argues that a POSA would not have known how to combine Evans and Mueller PCT and would not have known how to combine the variable and constant domains disclosed by those references. I addressed this argument above (¶¶59, 62) and in my original declaration. (EX1003, ¶¶151-156.) To summarize, the combination is an exceedingly simple one since Evans discloses full length variable regions and a POSA would know how to combine those with the full-length constant regions taught by Mueller PCT. (*Id.*)

76. In ¶254 of his declaration, Dr. Casadevall argues that Amgen's expert Dr. Balthasar used hindsight. This is not pertinent to my declaration because Dr. Casadevall makes no comments specific to my declaration, and in any event as I explained above any allegation of hindsight in my analysis is wrong. (*See* above ¶65.)

2. A POSA Would Have Had a Reasonable Expectation of Success

77. As I explained in my original declaration, a POSA would have had a reasonable expectation of success that the Mueller/Evans antibody would retain C5

binding. (EX1003, ¶¶152-155, 159; *see also id.* ¶133.) As explained further below in this section, I disagree with Dr. Casadevall's arguments regarding possible loss of C5 binding when subclass-switching from IgG4 to IgG2/G4.

78. As a first example, Thomas itself reports that changes to the constant domain in the 5G1.1 antibodies discussed in that reference, for example when going from Fab fragments to full length, did not affect C5 binding. (EX1010, 013.) I also provided testimony on this subject in my deposition. (ALXN2104, 70:15-71:4, 176:11-25.)

79. As a second example, Mueller's IgG4 to IgG2/G4 subclass switch had no effect on target binding. (EX1006, 015-016 (noting that changing the anti-VCAM antibody from an IgG4 to an IgG2/G4 did not impact its ability to bind to target or its avidity); EX1009, 014 (referring to discussion of the data presented at Fig. 14).) I also provided testimony on this subject in my deposition. (ALXN2104, 62:13-63:8, 175:8-25.) If further note that the Mueller 1997 reference confirms that the change from IgG4 to IgG2/G4 as disclosed in the Mueller publications actually does not involve a significant number of amino acid changes – providing still further reason why a POSA would have had a reasonable expectation of success that the IgG2/G4 antibody sequences provided by the prior art would bind to C5. (*See* EX1006, 016 (noting "the similarities between these two isotypes at the amino acid

level[.]”).)

80. A POSA would thus have had a reasonable expectation of success that the Evans/Mueller antibody would retain C5 binding, as I explained at my deposition. (ALXN2104, 175:8-177:4.) I have also examined Dr. Casadevall’s deposition transcript from the prior Amgen IPR, and note that Dr. Casadevall admitted that none of the examples that he argues show that constant domain changes can affect target binding pertaining to an IgG2/G4 antibody, or to a transition from an IgG4 antibody to an IgG2/G4 hybrid. (EX1101, 191:7-12, 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18.)

81. I note that Alexion also argues that there would have been immunogenicity concerns associated with an IgG2/G4 hybrid antibody. (POR, 38.) As noted above, any such concerns are directly contradicted by the prior art, which had already confirmed that eculizumab (disclosed by Tacken as a humanized IgG2/G4 antibody) did not trigger an immunogenic response in human patients. (EX1003, ¶¶48, 58; EX1013, 013.)

82. I have examined Dr. Casadevall’s declaration from the previous Amgen IPR of the ’504 patent on the Evans/Mueller PCT combination and reasonable expectation of success as discussed in this section, and I disagree with his opinions

as explained further below. (*See, e.g.*, ALXN2022, ¶¶257-258, 260-262.)

83. In ¶¶257-258 of his declaration, Dr. Casadevall simply rehashes his general arguments against the obviousness rationale of combining Evans and Mueller PCT (in view of Bell and Tacken) and wrongly contends that the literature taught that eculizumab was an IgG4 antibody. I have already addressed these arguments and my reasons for disagreeing with them above.

84. In ¶¶260-262 of his declaration, Dr. Casadevall again restates his concern that moving from an IgG4 subclass antibody to an IgG2/G4 subclass would not reasonably be expected to retain C5 binding. As already discussed above (¶¶77-81) I disagree. In addition to the prior art disclosing that the variable domain of 5G1.1 could tolerate changes to the constant domain without affecting C5 binding, and the teaching that Mueller's antibody was not affected in terms of target binding when going from IgG4 to IgG2/G4, a POSA would have known from Tacken that eculizumab was an IgG2/G4 and would have known from Bell that eculizumab was an anti-C5 antibody that had been successfully used to treat PNH. So a POSA would absolutely have had a reasonable expectation of success that, by constructing eculizumab from combining the teachings of Evans and Mueller PCT, the resulting antibody would retain C5 binding.

E. Grounds 2 and 4: Claim 6 Is Obvious over the Combinations of Grounds 1 and 3 Further Combined with Wang

85. I have reviewed Alexion's response document as relates to the dosing and formulation limitations of challenged claim 6. (POR, 48-52.) I disagree that these limitations were not obvious or add anything of patentable consequence to the antibody sequence and PNH treatment limitations of the claims. I explained these opinions in detail in my initial declaration. (EX1003, ¶¶144-150, 161.) I respond to Dr. Casadevall and Dr. Trout's opinions on these points below. (*See* ALXN2022, ¶¶189-191; ALXN2024, ¶¶64-91.)

86. I disagree that a POSA would have had any concern about the stability of eculizumab formulations for injection. For example, and as I previously explained, Bell expressly discloses "[f]ormulations" of eculizumab "suitable for injection" (referencing the Remington's standard) and reports on their successful use in the clinic. (EX1007, [0062]; EX1003, ¶¶94-98, 144-148; EX1062, ¶33.) Remington's Pharmaceutical Sciences is a standard reference for the preparation of pharmaceutical compositions widely known by a POSA in this field. Indeed, the challenged patent itself expressly references the very same Remington's Pharmaceutical Sciences text in its own disclosure of "[f]ormulations suitable for injection." (EX1001, 16:45-47; EX1062, ¶33.) A POSA reading Bell in view of Tacken would understand that Bell was discussing eculizumab as an IgG2/G4

antibody and teaching that it could be stably formulated for injection.

87. As I noted in my original declaration, Wang also taught stable eculizumab formulations at concentrations as high as 30 mg/ml, and 10 mg/mL was known to be a commonly used concentration for antibody formulations. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173]; EX1061, 014; EX1056-EX1060; EX1003, ¶¶148, 150.)

88. I further note that no single instance of any concerns relating to the stability of eculizumab has been identified in any of the many prior art publications reporting on the PNH clinical trials, some of which ran for two years. (EX1003, ¶58.) Thus, again a POSA would not have had any reason to be concerned that the eculizumab antibody reported in Bell and other clinical trials, which Tacken taught was an IgG2/G4 antibody, would be difficult to stably formulate. (EX1003, ¶¶149-150.) Finally, I note that none of the challenged claims require any particular level of stability, or recite any claim language relating to stability, which I understand is pertinent to the obviousness analysis because the claim should be judged according to its objective reach.

89. It appears that Alexion argues that the 30 mL (10 mg/mL) and 300 mg limitation of the claims were merely specific choices from among many options that the prior art made available to a POSA. (POR, 50-51.) My understanding is that

merely selecting one option from several taught by the prior art, especially in the absence of any unexpected results or reasons why the chosen option would be special, is not inventive. And as I explained in detail in my original declaration, 10 mg/mL and 300 mg *were* particularly attractive to a POSA from within these known ranges, because 10 mg/mL was a commonly used antibody concentration and because 300 mg was the best single use dose format that would be most appropriate for use in a mixed dosing schedule that had 600 and 900 mg components. (EX1003, ¶¶138, 148.)

90. And while I further agree that in a general sense stability of an antibody formulation is a relevant consideration and an important one, in this case there is simply no evidence from the prior art that a POSA would have had any need to balance stability against other factors such as convenience, ease of use, lack of waste, sterility, etc., because a POSA knew that eculizumab had already been successfully formulated and used in clinical trials. (EX1003, ¶138; EX1062, ¶28.)

91. I note in closing that Alexion did not submit any expert testimony specifically rebutting my opinions or those of Dr. Ippoliti regarding why the dosing and formulation limitations were obvious. Alexion does rely on the Trout declaration re-used from the Amgen IPR proceeding relating to the ’504 patent, which I address next.

92. I have reviewed the Trout Declaration as relied upon in Alexion's response brief. (ALXN2024, ¶¶64-91.) As discussed below, I do not agree with Dr. Trout that a POSA would not have had a motivation to combine the prior art of Ground 1 with a reasonable expectation as it pertains to the dosing and formulation limitations.

93. In ¶¶66-67, 69 of his declaration, Dr. Trout argues that neither Bell nor Wang disclose the complete amino acid sequence of eculizumab, and generally contends that POSA would not have known that an antibody with a sequence matching that of what is recited in the challenged claims had already been tested in clinical trials. But of course those sequences were disclosed as I previously explained by the Bowdish and Evans references, especially when viewed in combination with Mueller PCT and Tacken. (EX1003, ¶¶111-133.)

94. In ¶¶68 and 72 of his declaration, Dr. Trout contends that a POSA would not have believed that eculizumab had ever been successfully formulated for therapeutic use. But this is incorrect, because a POSA would know from Bell in view of Tacken that eculizumab, which is an IgG2/G4 antibody, had in fact been successfully used in human patients in clinical trials. (EX1003, ¶¶58, 94-98, 149-150.) Dr. Trout also places emphasis on the fact that an IgG2/G4 antibody had not previously been approved by the FDA, but this standard for motivation and

reasonable expectation of success goes far beyond the appropriate standard as I understand it. As I have previously explained, there was more than sufficient detail and evidence in the prior art for a POSA to have motivation and a reasonable expectation of success. I address Dr. Trout's other opinions concerning the Bell and Wang references below.

95. In ¶¶70-71 of his declaration, Dr. Trout generally argues about alleged uncertainty in connection with the formulation of antibodies and in particular asserts that a POSA would not have had any confidence in the ability to formulate eculizumab. First, as already noted, in the case of eculizumab as of March 2007, any such concerns would not have applied because the prior art already taught that the IgG2/G4 antibody eculizumab had been successfully formulated for injection and used in clinical trials, some of which ran for two years. (EX1003, ¶¶58, 94-98, 149-150.) Secondly, I disagree with Dr. Trout that antibody formulation was such an uncertain field that a POSA would not have had a reasonable expectation of success. Once again, it appears that Dr. Trout is applying the incorrect legal standard and arguing that a POSA would have required a virtual guarantee of success in order to proceed ("a POSA would not have <u>known</u>"), but as I understand what is required is a reasonable expectation of success. (ALXN2024, ¶71 (emphasis added).) And furthermore, by 2007 much was known about successful formulation of antibodies,

and there was no reason to think, again given the large number of clinical trial publications relating to eculizumab, that there would be any difficulty in formulating the antibody as a pharmaceutical composition. (EX1003, ¶¶55, 58; EX1052; EX1062, ¶¶25-26, 61.)

96. In ¶¶73-74 of his declaration, Dr. Trout argues that a POSA would have been concerned with whether a POSA relying on the sequences of Bowdish and Evans for the sequence of eculizumab could have been formulated as a solution. But as I previously explained, Bell expressly disclosed that eculizumab was delivered by intravenous infusion, which requires a solution be prepared. (EX1003, ¶138; EX1007, [0082].) I also previously explained that by 2007 it was commonplace for antibodies to be supplied in solution formulations that could be conveniently added to an IV bag for infusion. (EX1003, ¶148.) Dr. Trout also contends that pharmaceutical compositions are not necessarily supplied by the manufacturer as solutions but sometimes are supplied as lyophilized powders that are made into solutions prior to injection. I do not see why this distinction is meaningful for the challenged claims, which merely recite the common term "pharmaceutical composition" and say nothing about whether that composition might be supplied in a lyophilized powder form by the manufacturer – indeed if anything the claims are clear in their focus on the point of administration to a patient, since they recite the

language "for use in treating a patient." In other words, it appears that Dr. Trout is pointing to considerations that have nothing to do with the actual limitations of the challenged claims. And in any case, for the reasons already explained above, the prior art taught that antibodies were commonly supplied as solutions and the Bell reference specifically discloses the use of a solution formulation for IV infusion.

97. In ¶¶76-80 and 90, Dr. Trout argues that a POSA would not have been motivated to prepare eculizumab specifically in a 10 mg/mL concentration. As I previously explained in my declaration, I disagree. (EX1003, ¶148; EX1062, ¶¶55, 58-59.) As previously explained, a POSA would have known that 10 mg/ml was within the well-known range of concentrations of several FDA-approved antibody pharmaceutical compositions. (EX1061, 014 (Table 1); EX1056 (Campath), 013 (10 mg/ml); EX1057 (Erbitux) (2 mg/ml), 001; EX1058 (Herceptin), 001-02 (21mg/ml); EX1059 (Remicade), 001 (10 mg/ml); EX1060 (Rituxan), 001 (10 mg/ml).)

98. In ¶¶81-89 of his declaration, Dr. Trout presents his arguments concerning the Wang reference, and contends that it did not provide sufficient disclosure of dosing and formulation information, as well as stability data, to provide a POSA with motivation to combine and a reasonable expectation of success. I disagree. As previously explained, a POSA would have found the Wang reference

pertinent and would have obtained further motivation to combine and reasonable expectation of success from its teachings. (EX1003, ¶¶108-109, 148, 149-150; EX1062, ¶¶58-59, 60-61.) First, Dr. Trout focuses on Wang's teachings concerning nebulization, but this subject in Wang would not have lessened the relevance to a POSA of the fact that, in order to study formulation of eculizumab for nebulization, Wang first had to prepare an aqueous solution of eculizumab and study its stability and integrity.

99. A POSA would have understood 1) the teachings of Wang that specifically referenced the range of 1-30 mg/mL, 2) the express teaching that antibodies can be stably formulated from 1-200 mg/mL, and 3) the stability data showing that eculizumab in liquid formulations maintained its stability. (EX1003, ¶¶108-109, 148, 150; EX1044, Fig. 10, [0025], [0067], [0170]-[0173].) Specifically, the experimental examples disclosed in Wang that concern eculizumab formulations begin by referring to Fig. 10, which expressly discloses "Formulation 1" a range of 1 to 30 mg/mL. (EX1044, [0170], Fig. 10.) While Wang's [0170] references a mouse 5G1.1 antibody, the remaining related experiments in [0171]-[0173] all refer to eculizumab, expressly. Wang's experiments then go on to prepare such formulations of eculizumab – as aqueous solutions – at concentrations as high as 30 mg/mL, and confirm their stability and integrity through an aerosolization process.

(EX1044, [0171]-[0173], Figs. 12-15.) A POSA would have understood from these experiments that if eculizumab could maintain stability and integrity in an aqueous solution despite the stresses of an aerosolization procedure, it would also be stable in the initial aqueous solution. I further note that Dr. Ippoliti confirmed in her deposition that Wang specifically taught that eculizumab in aqueous solution was stable when examined by experiments using HPLC to monitor integrity of the drug. (EX2106, 59:20-60:3.) To the extent Dr. Trout seeks to add further limitations to the claim requiring a specific shelf life or stability level over some unspecified period of time (e.g., ALXN2024, ¶¶84, 87), again I note that Dr. Trout is applying the wrong standard and not examining the actual limitations of the challenged claims as written, which do not recite any particular requirements for shelf life or stability over some period of time. Finally, I note that Dr. Trout does not point to any evidence in the prior art concerning eculizumab, including the many references detailing its use in clinical trials involving IV infusion, in which any particular stability concerns were noted for eculizumab. Thus, in my opinion, Dr. Trout is improperly generalizing from his opinion that there can be no absolute guarantee of success for the formulation of every antibody, and arguing from this that a POSA would not have had a reasonable expectation of success.

100. Last, in ¶91 of his declaration, Dr. Trout argues that there was no reason

to formulate eculizumab in a 300 mg dose amount. As I previously explained, I disagree. (EX1003, ¶138; EX1062, ¶55.) In fact, 300 mg is clearly the most appropriate single dose for Bell's disclosed regimen of 600 mg and 900 mg, because a POSA would have been motivated to prepare a single dose formulation that could be easily scaled by arithmetic to reach those two common dose applications. (*Id.*) That a POSA might also think of *other*, less convenient, less scalable doses to prepare does not detract from the 300 mg dose option that would immediately recommend itself to a POSA. I also do not agree with Dr. Trout that the existence of multiple dosage forms for other FDA approved antibodies is pertinent here, and I note his examples involve very different dose ranges and situations in which the antibody may be dosed differently for different indications. Here, we have the clear 600/900 mg disclosures of Bell for the treatment of PNH, and a POSA would have been motivated to make a 300 mg dose for use in that treatment regimen. I have also reviewed the few paragraphs of the Casadevall Declaration cited by Alexion in connection with these issues (ALXN2022, ¶¶189-191). His brief opinions on these issues are entirely cumulative to Dr. Trout's opinions, which I have discussed and rebutted above.

F. Ground 5: Claims 1-5 and 7-10 Are Anticipated by Bell

101. Ground 5 relates to my argument that Bell inherently anticipates the

amino acid sequence limitations of the challenged claims. (EX1003, ¶¶162-168.) In its Response, Alexion primarily makes legal arguments and only cites to the declarations of Dr. Casadevall and Dr. Trout in two locations. (*See* POR, 56-66.) The section of Dr. Trout's declaration cited is the same one cited for Grounds 2 and 4 and pertains to his arguments on the dose and formulation limitations of Claim 6, to which I responded above. (*See* above Part II.E.)

102. Alexion cites ¶¶174-184 of Dr. Casadevall's declaration (POR, 66), which I have evaluated. I note initially that this citation does not make sense and seems to be in error because these paragraphs relate to his argument that claims 1-3 and 7-10 are not anticipated by the Hillmen `04 reference, which is not directly relevant or responsive to the Bell-based arguments I made for Ground 5 as noted above. (*See* ALXN2022, ¶¶174-184.)

103. Nevertheless, Dr. Casadevall in ¶¶174-184 argues that the Hillmen and Hill references do not anticipate because the use of the term "eculizumab" (which Bell also uses) is not necessarily a disclosure of the amino acid sequences corresponding to SEQ ID NOS:2 and 4 as recited in the challenged claims. As I explained in my previous declaration, I disagree. (EX1003, ¶¶162-168.) To begin with, Alexion has admitted more than once that the eculizumab used in the clinical trial reported in Bell (and elsewhere) was *in fact* the antibody with the amino acid

sequence in SEQ ID NOS:2 and 4. (EX1003, ¶163.) Beyond this the amino acid sequence of eculizumab was readily available to a POSA through either Bowdish and Evans or Evans and Mueller PCT, and a POSA would not have mistakenly thought that eculizumab was an IgG4 antibody. (EX1003, ¶¶164-165.)

104. Alexion also cites ¶¶195-199 of Dr. Casadevall's declaration. (POR, 60.) These paragraphs deal with the Bell reference and provide Dr. Casadevall's argument that a POSA would not have been motivated from Bell to make eculizumab from the disclosures of Bowdish and Evans. I already addressed the arguments in these paragraphs of Dr. Casadevall's declaration above in connection with Ground 1, and reiterate those points here. (*See* above ¶25-37.)

G. Alexion Failed to Show Any Secondary Considerations of Non-Obviousness

105. I note that Dr. Casadevall makes a single blanket statement that he believes that secondary considerations of nonobviousness support the validity of the '504 patent, although he does not explain in any detail why. (ALXN2105, ¶10.) He also cites to his prior declaration from an Amgen IPR (ALXN2022).

106. However, I also note that Alexion did not cite to <u>any</u> testimony from <u>any</u> expert in its discussion of secondary considerations in its Response. (*See* POR, 67-70.) Accordingly, it appears that Alexion does not intend to rely on any expert testimony for its secondary considerations arguments.

107. I also note that, based on the record available to it at that time (which has not substantively changed since then), the Board in this matter agreed with my opinion that Alexion had not shown the nonobviousness of the claims through any secondary considerations. (ID, 25-29.)

108. Accordingly, I maintain and reiterate my opinions regarding secondary considerations, as follows.

109. Alexion cannot argue secondary considerations of nonobviousness based on commercial success of its drug Soliris (i.e., eculizumab) because the use of eculizumab as a treatment for PNH was already in the prior art, and thus cannot be novel to the claims. As described above, prior art publications such as Bell, Hillmen 2004 and Hill 2005 disclosed successful treatment of PNH with eculizumab well before the priority date of 2007. (EX1003, ¶¶56-58.) Indeed, the use of eculizumab as a PNH therapy cannot be disputed as prior art to the ’504 patent. Moreover, Alexion also stated in 2002 that the prior art Evans patent is associated with the claimed invention of eculizumab. (EX1020; EX1023.) Given that the prior art disclosed the eculizumab sequence and its use in PNH therapy before 2007, evidence of commercial success cannot be derived from the fact that Soliris was commercially approved in 2007.

110. Alexion similarly cannot argue that the sequence of eculizumab solved

a long-felt and art-recognized need, because prior art publications, such as Bell, Hillmen 2004, and Hill 2005—which were all published at least 2-3 years before 2007—already disclosed use of eculizumab as a successful treatment for PNH. Therefore, as of March 2007, no long-felt need existed for a treatment for PNH such as Soliris (i.e., eculizumab). I understand that Soliris was not FDA-approved as a treatment for PNH until March 2007, but this does not mean that a long-felt need existed as of that time for secondary considerations purposes. This is because secondary considerations evidence must be novel with respect to the patent claim at issue, and the use of eculizumab as a treatment for PNH was indisputably not novel by March 2007.

111. Alexion also cannot argue nonobviousness based on industry praise because any evidence of industry recognition following the launch of Soliris as a successful treatment for PNH has no nexus with anything novel in the challenged claims. As described above, by 2007 there was nothing novel about the use of eculizumab for treating PNH. Further, there is no nexus between any prizes awarded for use of Soliris and the claimed invention because nothing suggests that any prize was awarded due to the sequences claimed in claim 1, as opposed to what was already known about eculizumab in the prior art.

112. Lastly, the fact that other companies are developing biosimilars of

Soliris should not be used as evidence of "copying." I have been informed that according to statutes and regulations, biosimilars are required to be "highly similar to the reference product," i.e., Soliris in this case. Since this similarity is required by law, I understand that development of biosimilars should not be entitled to weight in an obviousness analysis.

III. CONCLUSION

113. 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.

114. 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,

Jeffrey V. Ravetch, M.D., Ph.D.

EXHIBIT A

CURRICULUM VITAE

Name: Jeffrey V. Ravetch

Date and Place of Birth: May 3, 1951; New York, New York

Citizenship: United States

Residence: 500 Park Ave, New York, NY 10022

Education:

June 1973 - **B.S.**, Yale University, New Haven, CT
June 1978 - **Ph.D.,** Laboratory of Genetics (N. Zinder and P. Model), The Rockefeller University, New York, NY
June 1979 - **M.D.,** Cornell University Medical College, New York, NY

Postdoctoral Training:

1979 - 1982 Laboratory of Molecular Genetics (P. Leder), NICHD, NIH, Bethesda, MD

Positions and Appointments:

1997- **Theresa and Eugene M. Lang Chair,** The Rockefeller University
1996- **Professor**, The Rockefeller University
1993 - 1996 **Adjunct Professor**, Department of Microbiology and Immunology, Jefferson Medical College and Jefferson Cancer Institute
1990 - 1996 **Attending**, Division of Hematologic Oncology, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases
1990 - 1996 **Member,** Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Professor, Cornell University Medical College
1986 - 1990 **Associate Attending,** Division of Medical Oncology, Hematology-Lymphoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center
1986 - 1990 **Associate Member,** Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Associate Professor, Cornell University Medical College
1984 - 1987 **Guest Investigator,** Laboratory of Cellular Physiology and Immunology, The Rockefeller University
1982 - 1986 **Assistant Member,** Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Assistant Professor, Cornell University Medical College
1979 - 1982 **Research Associate,** Laboratory of Molecular Genetics, NICHD, National Institutes of Health
1973 - 1979 **Biomedical Fellow,** The Rockefeller University
1972 - 1973 **Teaching Assistant,** Dept. of Chemistry, Yale University

Honors and Awards:

NSF Summer Research Fellowships, 1971, 1972
Cum laude, Yale College, 1973
Charles E. Culpeper Fellow, 1983-1985
Pew Scholar, 1985-1989
Burroughs-Wellcome Award in Molecular Parasitology, 1986
Irma T. Hirschl/Monique Weill-Caulier Trust Career Scientist Award, 1986
Boyer Research Award, Memorial Sloan-Kettering Cancer Center, 1988
Kunkel Lecturer, Rockefeller University, 1996
NIH MERIT Award, 1997
Ecker Lecturer, Case Western Reserve University, 2000
Lee J. Howley, Jr. Award, 2004
AAI-Huang Foundation Meritorious Career Award, 2005
Member, National Academy of Sciences, 2006
William B. Coley Award, Cancer Research Institute, 2007
Member, Institute of Medicine, 2007
Fellow, American Academy of Arts and Sciences, 2008
Fellow, American Association for the Advancement of Science, 2008
R.E. Dyer Lecture, NIH, 2010
Grabar Lecture, French Society of Immunology, 2010
Gairdner International Award, 2012
Sanofi-Institut Pasteur Award, 2012
Heidelberger-Kabat Lecture, Columbia University, 2013
Fahey/Rose Founders Lecture, Clinical Immunology Society, 2013
Honorary doctorate Friedrich-Alexander-University Erlangen-Nurenberg, 2013
Josephson Lecture, Downstate Medical College, 2014
Wolf Prize in Medicine, 2015
Distinguished Lecturer, Academia Sinica, 2015
Benacerraf Lecture, Harvard Medical School, 2016
Ross Prize in Molecular Medicine, 2017
Robert Koch Award, 2018
William Paul Memorial Award, 2021

Patents:

5,116,965-Methods of obtaining histidine-rich protein genes of plasmodia
5,723,593-Diagnostic assay for Charcot Marie Tooth disease type 1B
5,728,377-Methods and compositions Incorporating IP-10
5,824,487-Method for screening for targets for anti-inflammatory or anti-allergic agents.
5,876,927-Nucleic acid diagnostic assay for Charcot-Marie-Tooth Disease type IB
5,877,396-Mice mutant for Fc Receptors and method of treating autoimmune disease.
6,676,927-Animal model and methods for its use in the selection of cytotoxic antibodies
7,038,031-DNA encoding FcγR receptor protein on NK cells.
7,416,726-Enhancement of antibody-mediated immune responses
7,846,744-Methods of identifying anti-inflammatory compounds
8,470,318-Polypeptides with enhanced anti-inflammatory properties
8,470,321-Antibodies specific for the protofibril form of beta-amyloid protein

8,618,251-Fc mutants
8,815,237-Aglycosylated immunoglobulin mutant
9,134,310 Methods of identifying anti-inflammatory compounds
9,340,607-Antibodies specific for the protofibril form of beta-amyloid protein
9,481,724-hDC-SIGN binding peptides
9,587,025 Non-sialylated anti-inflammatory polypeptides
9,657,101 Fc mutants
9,845,358 Anti-inflammatory polypeptides
10,167,332 Polypeptides with enhanced anti-inflammatory and decreased cytotoxic properties
10,300,127 Immune complex
10,479,838 Antibodies to CD40 with enhanced agonist activity

Other Activities:

National

Ad hoc member, Immunobiology Study Section, 1986-1990
Ad hoc member, Tropical Medicine and Parasitology Study Section, 1988-1990
Member, Allergy and Immunology Study Section, 1990-1994
Member, Blood Diseases Advisory Panel of The New York Community Trust, 1990-1996
Founder and Organizer (with D. Wirth and L. van der Ploeg), Annual Woods Hole Molecular Parasitology Meeting, 1990-1992
NIH Task Force on Immunology and Aging, 1994
Institute of Medicine, Nat'l Academy of Sciences, Committee on Malaria Vaccines, 1995
AAI, American Association of Immunologists, Public Affairs Committee, 2003-2005

Editorial

Advisory Editor, The Journal of Experimental Medicine
Transmitting Editor, International Immunology

Scientific Consulting and Advisory Boards

Biohaven Pharmaceuticals
NuvigTherapeutics
Jasper Therapeutics
Seismic Pharmaceuticals
Vir Biotherapeutics

Professional Memberships:

American Society for Biochemistry and Molecular Biology
American Society for Cell Biology
American Society for Clinical Investigation
Harvey Society
AAAS
AAI

Home Address: 500 Park Ave., 39th floor
New York, NY 10022

Tel. #: (212) 319-3117

Office Address: The Rockefeller University
1230 York Ave., Box 98
New York, NY 10021

Tel. #: (212) 327-7321

E-Mail: ravetch@rockefeller.ed

Military Services: 1979-1982 USPHS Surgeon (04)

Bibliography

1. **Ravetch, J.V.**, Gralla, J. and Crothers, D.M. (1974) Thermodynamic and kinetic properties of short RNA helices: the oligomer series A_nGCU_n. *Nucleic Acids Research* 1:109-127. PMC343329
2. **Ravetch, J.V.** and Jakes, K.S. (1976) Intact 3' end of 16S rRNA is not required for specific mRNA binding. *Nature* 262:150-153.
3. **Ravetch, J.V.**, Model, P. and Robertson, H.D. (1977) Isolation and characterization of the <x174 ribosome binding sites. *Nature* 265:698-702.
4. **Ravetch, J.V.**, Horiuchi, K., and Model, P. (1977) Mapping of bacteriophage f1 ribosome binding sites to their cognate genes. *Virology* 81:341-351.
5. **Ravetch, J.V.**, Horiuchi, K. and Zinder, N.D. (1977) Nucelotide sequences near the origin of replication of bacteriophage f1. *Proc. Natl. Acad. Sci. USA* 74:4219-4222.
6. **Ravetch, J.V.**, Horiuchi, K. and Zinder, N.D. (1978) Nucleotide sequence of the recognition site for the restriction-modification enzyme of *Escherichia coli B*. *Proc. Natl. Acad. Sci. USA* 75:2266-2270. PMC392533
7. Horiuchi, K., **Ravetch, J.V**. and Zinder, N.D. (1978) DNA replication of bacteriophage f1 in vivo. *Cold Spring Harbor Symposium on Quantitative Biology*, Vol. 43.
8. **Ravetch, J.V.**, Horiuchi, K. and Zinder, N.D. (1979) DNA sequence analysis of the defective interfering particles of bacteriophage f1. *J. Mol. Biol*. 128:305-318.
9. **Ravetch, J.V.**, Ohsumi, M., Model, P., Vovis, G.F., Fischoff, D. and Zinder, N.D. (1979) Organization of a hybrid between phage f1 and plasmid pSC101. *Proc. Natl. Acad. Sci. USA* 76:2195-2198. PMC383564
10. **Ravetch, J.V.**, Kirsch, I.R. and Leder, P. (1980) Evolutionary approach to the question of immunoglobulin heavy chain switching: Evidence from cloned human and mouse genes. *Proc. Natl. Acad. Sci. USA* 77:6734-6738. PMC350363
11. Korsmeyer, S.J., Hieter, P., **Ravetch, J.V.**, Poplack, D., Waldmann, T. and Leder, P. (1981) Developmental hierarchy of immunoglobulin gene rearrangements in human leukemic pre-B cells. *Proc. Natl. Acad. Sci. USA* 78:7096-7100. PMC349202
12. Kirsch, I., **Ravetch, J.V**., Kwan, S.-P., Max, E.E., Ney, R.L. and Leder, P. (1981) Multiple immunoglobulin switch region homologies outside the heavy chain constant region locus. *Nature* 292:585-587.
13. Siebenlist, U., **Ravetch, J.V.**, Korsmeyer, S., Waldmann, T. and Leder, P. (1981) Human immunoglobulin D segments encoded in tandem multigenic families. *Nature* 294:631-635.
14. **Ravetch, J.V.**, Siebenlist, U., Korsmeyer, S., Waldmann, T. and Leder, P. (1981) The structure of the human immunoglobulin μ locus: characterization of embryonic and rearranged J and G genes. *Cell* 27:583-591.
15. Korsmeyer, S.J., Arnold, A., Bakhshi, A., **Ravetch, J.V.**, Siebenlist, U., Hieter, P.A., Sharrow, S.O.,LeBien, T.W., Kersey, J.H., Poplack, D.G., Leder, P. and Waldmann,T.A. (1983) Immunoglobulin gene rearrangement and cell surface antigen expression in acute lymphocytic leukemias of T-Cell and B-Cell precursor origins. *J. Clin. Invest*. 71:301-313. PMC436868
16. Waldmann, T.A., Korsmeyer, S.J., Hieter, P.A., **Ravetch, J.V.**, Broder, S. and Leder, P. (1983) Regulation of the humoral immune response: from immunoglobulin genes to regulatory T cell networks. *Fed. Proc*. 42:2498-2503.
17. Shin, H.-S., Flaherty, L., Artzt, K., Bennett, D. and **Ravetch, J.V.** (1983) Inversion in the H-2 complex of t-Haplotypes in mice. *Nature* 306:380.
18. **Ravetch, J.V.**, Feder, R., Pavlovec, A. and Blobel, G. (1984) Primary structure and genomic organization of the histidine-rich protein of the malaria parasite *Plasmodium lophurae*. *Nature* 312:616.

19. **Ravetch, J.V.**, Kochan, J. and Perkins, M. (1985) Isolation of the gene for a glycophorin-binding protein implicated in erythrocyte invasion by a malaria parasite. *Science* 227:1593-1597.
20. Luster, A.D., Unkeless, J.C. and **Ravetch, J.V**. (1985) y-interferon transcriptionally regulates an early-response gene with homology to platelet proteins. *Nature* 315:672-676.
21. Bakshi, A., Guglielmi, P., Siebenlist, U., **Ravetch, J.V**., Jensen, J.P. and Korsmeyer, S.J. (1986) A DNA insertion/deletion necessitates an aberrant RNA splice accounting for a μ heavy chain disease protein. *Proc. Natl. Acad. Sci. USA* 83:2689-2693. PMC323365
22. Kochan, J., Perkins, M. and **Ravetch, J.V.** (1986) A tandemly repeated sequence determines thebinding domain for an erythrocyte receptor binding protein of *P. falciparum*. *Cell* 44:689-696.
23. Pologe, L. and **Ravetch, J.V.** (1986) A chromosomal rearrangement in a *P. falciparum* histidine-rich protein gene is associated with the knobless phenotype. *Nature* 322:474-477.
24. Portnoy, D.A., Erickson, A.H., Kochan, J., **Ravetch, J.V**. and Unkeless, J.C. (1986) Cloning and characterization of a mouse cysteine proteinase. *J. of Biol. Chem*. 261:14697-14703.
25. **Ravetch, J.V.**, Luster, A., Weinshank, R., Kochan, J., Pavlovec, A., Portnoy, D., Hulmes, J., Pan, Y-C. and Unkeless, J. (1986) Structural heterogeneity and functional domains of murine immunoglobulin G Fc receptors. *Science* 234:718-725.
26. Luster, A., Jhanwar, S., Chaganti, R.S.K., Kersey, J., and **Ravetch, J.V**. (1987) Interferon-inducible gene maps to a chromosomal band associated with a (4;11) translocation in acute leukemia cells. *Proc. Natl. Acad. Sci. USA* 84:2868-2871. PMC304761
27. Pologe, L., Pavlovec, A., Shio, H. and **Ravetch, J.V.** (1987) Primary structure and subcellular localization of the knob-associated histidine-rich protein of *Plasmodium falciparum*. *Proc. Natl.Acad. Sci. USA* 84:7139-7143. PMC299245
28. Luster, A.D. and **Ravetch, J.V.** (1987) Genomic characterization of gamma-interferon-inducible gene (IP-10) and identification of an interferon-inducible hypersensitive-site. *Mol. Cell. Biol*. 7:3723-3731. PMC368020
29. Luster, A.D. and **Ravetch, J.V.** (1987) Biochemical characterization of a y interferon inducible cytokine (IP-10). *J. Exp. Med*. 166:1085-1097.
30. Weinshank, R.L., Luster, A.D. and **Ravetch, J.V.** (1988) Function and regulation of a murine macrophage-specific IgG Fc receptor, FcyR-a. *J. of Exp. Med*. 167:1909-1925.
31. Luster, A.D., Weinshank, R.L. and **Ravetch, J.V.** (1988) Molecular and biochemical characterization of a novel y-interferon-inducible protein. *J. of Biol. Chem*. 263:12036-12043.
32. Pologe, L.G. and **Ravetch, J.V.** (1988) Large deletions result from breakage and healing of *P. falciparum* chromosomes. *Cell* 55:869-874.
33. Perussia, B., Tutt, M.M., Qiu, W.Q., Kuziel, W.A., Tucker, P.W., Trinchieri, G., Bennett, M., **Ravetch, J.V.** and Kumar, V. (1989) Murine natural killer cells express functional Fcy Receptor II encoded by the FcyRa gene. *J. Exp. Med*. 170:73-86
34. **Ravetch, J.V.** and Perussia, B. (1989) Alternative membrane forms of FcyRIII(CD16) on human natural killer cells and neutrophils: Cell-type specific expression of two genes that differ in single nucleotide substitutions. *J. Exp. Med*. 170:481-497.
35. Brooks, D., Qiu, W.Q., Luster, A.D. and **Ravetch, J.V.** (1989) Structure and expression of human IgG FcRII(CD32): Functional heterogeneity is encoded by the alternatively spliced products of multiple genes. *J. Exp. Med*. 170:1369-1385.
36. Kurosaki, T. and **Ravetch, J.V.** (1989) A single amino acid substitution in the GPI attachment domain is responsible for the alternative membrane anchoring of FcyRIII(CD16). *Nature* 342:805-807.
37. Pologe, L.G., de Bruin, D. and **Ravetch, J.V**. (1990) A and T homoplymeric stretches

mediate a DNA inversion in *Plasmodium falciparum* which results in loss of gene expression. *Mol. Cell. Biol*. 10:3243-3246. PMC360690

38. Qiu, W.Q., de Bruin, D., Brownstein, B.H., Pearse, R., and **Ravetch, J.V.** (1990) Organization of the human and mouse low-affinity FcγR genes: Duplication and Recombination. *Science* 248:732-735.
39. Perussia, B. and **Ravetch, J.V**. (1991) FcγRIII(CD16) on human macrophages is a functional product of the FcγRIII-2 gene. *Eur. J. Immunol*. 21:425-429.
40. Kurosaki, T., Gander, I. and **Ravetch, J.V.** (1991) A subunit common to an IgG Fc receptor and the T cell receptor mediates assembly through different interactions. *Proc. Natl Acad. Sci. USA*, 88:3837-3841. PMC51548
41. Seykora, J., **Ravetch, J.V.** and Aderem, A. (1991) Cloning and molecular characterization of the murine macrophage "68-kDa" protein kinase C substrate, and its regulation by bacterial lipopolysaccharide. *Proc. Natl Acad. Sci. USA*, 88:2505-2509. PMC51261
42. Pearse, R., Feinman, R. and **Ravetch, J.V**. (1991). Characterization of the promoter of the human gene encoding the high-affinity IgG receptor: Transcriptional induction by γ-interferon is mediated through common DNA response elements. *Proc. Natl Acad. Sci. USA,* 88:11305-11309. PMC53123
43. Kurosaki, T., Gander, I., Wirthmueller, U. and **Ravetch, J.V.** (1992). The □ subunit of the FcεRI is associated with the FcγRIII on mast cells. *J. Exp. Med*., 175:447-451.
44. Wirthmueller, U., Kurosaki, T., Murakami, M. and **Ravetch, J.V.** (1992). Signal transduction by FcγRIII(CD16) is mediated through the γ chain, *J. Exp. Med*., 175:1381-1390.
45. Lanzer, M., de Bruin, D. and **Ravetch, J.V**. (1992). Transcription mapping of a 100 kb locus of *P. falciparum* identifies an intergenic region in which transcription terminates and reinitiates, *EMBO*, 11:1949-1955. PMC556654
46. Schenkman, S., Kurosaki, T. **Ravetch, J.V.,** and Nussenzweig, V. (1992) Evidence for the participation of the Ssp-3 antigen in the invasion of non-phagocytic mammalian cells by *Trypanosoma cruzi*, *J. Exp. Med*., 175:1635-1641.
47. Lanzer, M., de Bruin, D. and **Ravetch, J.V.** (1992) A sequence element associated with the *Plasmodium falciparum* KAHRP gene is the site of developmentally regulated protein interactions, *Nucl.Acids Res*., 20:3051-3056. PMC312436
48. de Bruin, D., Lanzer, M. and **Ravetch, J.V.** (1992) Characterization of yeast artificial chromosomes from *Plasmodium falciparum*: Construction of a stable, representative library and cloning telomeric DNA fragments, *Genomics,* 14:332-339.
49. Lanzer, M., de Bruin, D. and **Ravetch, J.V.** (1993). Cloning of a complete *Plasmodium falciparum* chromosome reveals transcriptional differences in polymorphic and conserved domains, *Nature,* 361:654-657.
50. Salcedo, T.W., Kurosaki, T., Kanakaraj, P., **Ravetch, J.V.** and Perussia, B. (1993) Physical and functional association of $p56^{lck}$ with FcγRIIIA (CD16) in Natural Killer cells, *J. Exp. Med.,* 177:1475-1480.
51. Pearse, R.N., Feinman, R., Darnell, J.E., Jr., and **Ravetch, J.V.** (1993) IFN-γ induction of FcγRI transcription requires assembly of a complex which includes a 91 kDa DNA binding protein, *Proc. Natl. Acad. Sci., USA*, 90:4314-4318. PMC46497
52. Sarris, A., Broxmeyer, H., Wirthmueller, U., Karasavvas, N., Cooper, S., Lu, L., Krueger, J., and **Ravetch, J.V.** (1993) Human interferon-inducible protein 10: Expression and purification of recombinant protein demonstrate inhibition of early human hematopoietic progenitors, *J. Exp. Med*., 178:1127-1132.

53. Muta, T., Kurosaki, T., Sanchez, M., Misulovin, Z., Nussenzweig, M., and **Ravetch, J.V.** (1994) A 13 amino acid motif in the cytoplasmic domain of FcγRIIB modulates B-cell receptor signalling. *Nature*, 368:70-73.
54. Su, Y., Brooks, D., Li, L., Lepercq, J., Trofatter, J., **Ravetch, J.**, and Lebo, R. (1993) Peripheral myelin protein zero gene mutated in Charcot-Marie-Tooth type 1B patients, *Proc. Natl Acad. Sci., USA*, 90:10856-10860. PMC47877
55. de Bruin, D., Lanzer, M., and **Ravetch, J.V.** (1994) Conserved arrays of repetitive sequences in the subtelomeric regions of *Plasmodium falciparum* chromosomes promote genetic diversity. *Proc. Natl. Acad. Sci., USA,* 91:619-623. PMC43000
56. Takai, T., Li, M., Sylvestre, D., Clynes, R., and **Ravetch, J.V**. (1994) FcR γ chain deletion results in pleiotropic effector cell defects. *Cell*, 76:519-529.
57. Feinman, R., Qiu, W.Q., Pearse, R.N., Nikolajczyk, B.S., Sen, R., Sheffery, M., and **Ravetch**, **J.V.** (1994) PU.1 and an HLH family member contribute to the myeloid-specific transcription of the FcγRIIIA promoter. *EMBO,* 13:3852-3860. PMC395298
58. Sylvestre, D.L. and **Ravetch, J.V**. (1994) Fc receptors initiate the Arthus reaction: Redefining the inflammatory cascade. *Science*, 265:1095-1098.
59. Lanzer, M., Wertheimer, S.P., de Bruin, D. and **Ravetch, J.V**. (1994) Chromatin structure determines the sites of chromosome breakages in *Plasmodium falciparum*. *Nucl. Acids Res*., 22:3099-3103. PMC310281
60. Lanzer, M., de Bruin, D., Wertheimer, S.P., and **Ravetch, J.V.** (1994) Transcriptional and nucleosomal characterization of a subtelomeric gene cluster flanking a site of chromosomal rearrangements in *Plasmodium falciparum*. *Nucl.Acids Res.*, 22:4176-82.
61. Clynes, R., and **Ravetch, J.V**. (1995) Cytotoxic antibodies trigger inflammation through Fc receptors. *Immunity*, 3:21-26. PMC331913
62. Rubio, J.P., Triglia, T., Kemp, D.J., de Bruin, D., **Ravetch, J.V.** and Cowman, A.F. (1995) A YAC contig map of *Plasmodium falciparum* chromosome 4; Transcriptional analysis and characterization of a DNA amplification between two recently separated isolates. *Genomics*, 26: 192-198.
63. Su, X-z, Heatwole, V., Wertheimer, S., Guinet, F., Herrfeldt, J.A., Peterson, D.S., **Ravetch, J.V.** and Wellems,T.E. (1995) The large diverse gene family *var* encodes proteins involved in cytoadherence and antigenic variation of *Plasmodium falciparum*-infected erythrocytes. *Cell*, 82:89-100.
64. Park, S.Y., Arase, H., Wakizaka, K., Hirayama, N., Masaki, S., Sato, S., **Ravetch, J.V.** and Saito, T.(1995) Differential contribution of the FcRγ chain to the surface expression of the T cell receptor among T cells localized in epithelia: analysis of the FcRγ deficient mice. *Eur. J. Immun*., 25(7):2107-10.
65. Economides, A.N., **Ravetch, J.V.**, Yancopolous, G.D. and Stahl, N (1995) Designer Cytokines: Targetting actions to cells of choice. *Science* 270: *1351-1353.*
66. Li, M., Wirthmueller, U. and **Ravetch, J.V.** (1995) Reconstitution of human FcγRIII cell-type specificity in transgenic mice, *J. Exp. Med.*, 183: 1259-1263
67. Seykora, J.T., Myat, M.M. Allen, L-A, **Ravetch, J.V.** and Aderem, A. (1996) Molecular determinants of the myristoyl-electrostatic switch of MARCKS, *J. Biol.Chem.,* 271: 18797-802
68. Takai, T., Ono, M., Hikida, M., Ohmori, H. and **Ravetch, J.V**. (1996) Augmented humoral and anaphylactic responses in FcγRII-deficient mice, *Nature*, 379:346-349.
69. Sylvestre, D., Clynes, R., Ma, M., Warren, H., Carroll, M. and **Ravetch, J.V.**(1996) IgG

mediated inflammatory responses develop normally in complement deficient mice, *J. Exp. Med*, 184:2385-2392. PMC2196366

70. Sylvestre, D. and **Ravetch, J.V.** (1996) A dominant role for mast cell Fc receptors in the Arthus reaction, *Immunity*, 5: 387-390
71. Ono, M., Bolland, S., Tempst, P. and **Ravetch, J.V.**(1996) The role of the inositol phosphatase SHIP in negative regulation of the immune system by the receptor FcyRIIB, *Nature* 383: 263-266.
72. Heiken, H., Schulz, R-J., **Ravetch, J.V.**, Reinherz, E. L., and Koyasu,S. (1996) T lymphocyte development in the absence of FcERIy subunit: analysis of thymic dependent and independent a-□ and y-8 pathways, *Eur.J.of Immunol.* 26:1935-1943.
73. Vasovic, L.V., Dyall R., Clynes, R., **Ravetch, J.V.** and Nikolic-Zugic, J.(1997) Synergy between an antibody and $CD8^+$ cells in eliminating an established tumor, *Eur. J of Immunol.,* 27:374-82.
74. Miyajuma, I., Dombrowicz, D., Martin, T. R., **Ravetch, J.V.,** Kinet, J-P., and Galli, S. J. (1997) Systemic anaphylaxis in the mouse can be mediated largely through IgG_1 and FcyRIII. Assessment of the cardiopulmonary changes, mast cell degranulation, and death associated with active or IgE- or IgG_1 dependent passive anaphylaxis, *J. of Clin. Invest.* 99:901-914. 507898
75. Dombrowcz, D., Flamand, V., Miyajima, I., **Ravetch, J. V.,** Galli, S. J., and Kinet, J.-P. (1997) Absence of FcERIa chain results in upregulation of FcyRIII-dependent mast cell degranulation and anaphylaxis. Evidence of competition between FcERI and FcyRIII for limiting amounts of FcR□ and y chains. *J. of Clin. Invest.,* 99:915-925. PMC507899
76. Ono, M., Okada, H., Bolland, S., Yanagi, S., Kurosaki, T. and **Ravetch, J.V.** (1997) Deletion of SHIP or SHP-1 reveals two distinct pathways for inhibitory signaling, *Cell,* 90:293-301.
77. Vora, K.A., **Ravetch, J.V.** and Manser, T. (1997) Amplified follicular immune complex deposition in mice lacking the Fc receptor y-chain does not alter maturation of the B Cell response. *J. Immunol*. 159:2116-2124.
78. Jankovic, D., Cheever, A.W., Kullberg, M.C., Wynn, T.A., Yap, G., Caspar, P., Lewis, F.A., Clynes, R., **Ravetch, J.,** and Sher, A. (1998) CD4+ T cell-mediated granulomatous pathology in schistosomiasis is down-regulated by a B lymphocyte-dependent mechanism requiring Fc receptor signalling. *J. Exp. Med*., 187:619-629. PMC2212140
79. Clynes, R., Takechi, Y., Moroi, Y., Houghton, A. and **Ravetch, J.V**. (1998) Fc Receptors are required in passive and active immunity to melanoma. *Proc. Nat'l Acad. Sci.., USA*, 95:652-656. PMC18475
80. Shores, E., Kawabe, K., Ono, M., Sommers, C.L., Tran, T., Liu, K., Udey, M., **Ravetch, J**. and Love, P.E. (1998) T cell development in mice lacking all TCR-t; family members (t;, 17, and FcERIy). *J. Exp. Med,* 187:1093-1101. PMC2212212
81. Clynes, R., Dumitru, C. and **Ravetch, J.V.** (1998) Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis. *Science* 279:1052-54..
82. Yuan, R. Clynes, R., Oh, J., **Ravetch, J.V**. and Scharff, M.D. (1998) Antibody-mediated modulation of *Cryptococcus neoformans* infection is dependent on distinct Fc receptors and IgG subclasses. *J. Exp. Med.,* 187:641-648. PMC2212141
83. Bolland, S., Pearse, R., Kurosaki, T. and **Ravetch, J.V.** (1998) SHIP modulates immune receptor responses by regulating membrane association of BTK. *Immunity,* 8:509-516.
84. Okada, H., Bolland, S., Hashimoto, A., Kurosaki, M., Iino, M., **Ravetch, J.V.** and Kurosaki, T. (1998). Role of the inositol phosphatase SHIP in B cell receptor-induced Ca^{2+}

oscillatory response. *J. Immunol.* 161:5129-5132.
85. Suzuki, Y., Shirato, I., Okumura, K., **Ravetch, J.V**., Takai, T., Tomino, Y., and Ra, C.S. (1998) Distinct contribution of Fc receptors and angiotensin II-dependent pathways in anti-GBM glomerulonephritis. *Kidney Int*. 54:1166-1174.
86. Clynes, R., Maizes, J.S., Guinamard, R., Ono, M., Takai, T., and **Ravetch, J.V.** (1999) Modulation of immune complex-induced inflammation *in vivo* by the coordinate expression of activation and inhibitory Fc receptors. *J. Exp. Med.,* 189:179-185. PMC1887693
87. Yuasa, T., Kubo, S., Yoshino, T., Ujike, A., Matsumura, K., Ono, M., **Ravetch, J.V**. and Takai, T. (1999) Deletion of FcγRIIB renders H-2^b mice susceptible to collagen-induced arthritis. *J. Exp. Med.,* 189:187-194. PMC1887699
88. Kubagawa, H., Chen, C.-C., Ho, L., Shimada, T., Gartland, L., Mashburn, C., Uehara, T., **Ravetch, J.V.** and Cooper, M.D. (1999) Biochemical nature and cellular distribution of the Paired Immunoglobulin-like Receptors, PIR-A and PIR-B. *J. Exp. Med.* 189:309-317. PMC2192985
89. Ujike, A., Ishikawa, Y., Ono, M., Yuasa, T., Yoshino, T., Fukumoto, M., **Ravetch, J.V**., and Takai, T. (1999) Modulation of IgE-mediated systemic anaphylaxis by low affinity Fc receptors for IgG. *J. Exp. Med.,* 189:1573-1579.
90. Pearse, R.N., Kawabe, T., Bolland, S., Kurosaki, T., and **Ravetch, J.V.** (1999) SHIP recruitment attentuates FcγRIIB induced B cell apoptosis. *Immunity* 10:753-760.
91. Guinamard, R., Signoret, N., Masamichi, I., Marsh, M., Kurosaki, T. and **Ravetch, J.V**. (1999) B cell antigen receptor engagement inhibits SDF-1α chemotaxis and promotes PKC-induced internalization of CXCR4. *J. Exp. Med.* 189:1461-1466. PMC2193069
92. Qin, D., Wu, J., Vora, K., **Ravetch, J.V**., Szakal, A.K., Manser, T. and Tew, J.G. (2000) FcγRIIB on follicular dendritic cells regulates the B cell recall response. *J. Immunology,* 164:6268-6275.
93. Nakamura, A., Yuasa, T., Ujike, A., Ono, M., Nukiwa, T., **Ravetch, J.V.** and Takai, T. (2000) FcγRIIB-deficient mice develop Goodpasture's Syndrome upon immunization with Type IV collagen: a novel murine model for autoimmune GBM disease. *J. Exp. Med.*, 191:899-905. PMC2195851
94. Jimack, L.F., Reininger, L., Chicheportiche, Y., Clynes, R., **Ravetch, J.V.,** Honjo, T., and Izui, S. (1999) High pathogenic potential of low-affinity autoantibodies in experimental autoimmune hemolytic anemia. *J. Exp. Med.* 190:1689-1696. PMC2195740
95. Clynes, R.A., Towers, T.L., Presta, L.G. and **Ravetch, J.V**. (2000) Inhibitory Fc receptors modulate *in vivo* cytotoxicity against tumor targets. *Nature Med*. 6:443-446.
96. Guinamard, R., Okigaki, M., Schlessinger, J. and **Ravetch, J.V.** (2000) Absence of marginal zone B cells in Pyk-2 deficient mice defines their role in the humoral response. *Nature Immunology,* 1:31-35.
97. Bolland, S. and **Ravetch, J.V**. (2000) Spontaneous autoimmune disease in FcγRIIB deficient mice results from strain-specific epistasis. *Immunity,* 13:277-285.
98. Samuelsson, A., Towers, T. and **Ravetch, J.V.** (2001) Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science*, 291:484-486.
99. Hawiger, D., Inabe, K., Dorsett, Y., Guo, M., Mahnke, K., Rivera, M., **Ravetch, J.V**., Steinman, R. and Nussenzweig, M. (2001) Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions in vivo. *J. Exp. Med*. 194:769-779. PMC2195961
100. Khalil, M., Inaba, K., Steinman, R., **Ravetch, J.** and Diamond, B. (2001) T cell studies in a

peptide-induced model of systemic lupus erythematosus. *J. Immunol.,* 66:1667-1674.
101. Bolland, S., Yim, Y-S., Tus, K., Wakeland, E.K. and **Ravetch, J.V**. (2002) Genetic modifiers of SLE in FcγRIIB$^{-/-}$ mice. *J. Exp. Med*. 195:1167-1174. PMC2193704
102. Kalergis, A. and **Ravetch, J.V**. (2002) Inducing tumor immunity through the selective engagement of activating Fcγ receptors on dendritic cells. *J. Exp. Med*. 195:1653-1659. PMC2193555
103. Trcka, J., Moroi, Y., Clynes, R.A., Goldberg, S.M., Bergtold, A., Perales, M-A., Ma, M., Ferrone, C.R., Carroll, M.C., **Ravetch, J.V**. and Houghton, A.N. (2002) Redundant and alternative roles for activating Fc Receptors and complement in an antibody-dependent model of autoimmune vitiligo. *Immunity,* 16:861-868.
104. Green, S.K., Karlsson, M.C.I., **Ravetch, J.V**. and Kerbel, R.S. (2002) Disruption of cell-cell adhesion enhances antibody-dependent cellular cytotoxicity: Implications for antibody-based therapeutics of cancer. *Cancer Research* 62:6891-6900.
105. Wang, C., Khalil, M., **Ravetch, J**. and Diamond B. (2003) The naive B cell repertoire predisposes to antigen-induced systemic lupus erythematosus. *J. Immunol.,* 170:4826-4832.
106. Bruhns, P., Samuelsson, A., Pollard, J. and **Ravetch, J.V**. (2003) Colony stimulating factor-1-dependent macrophages are responsible for IVIG protection in antibody-induced autoimmune disease. *Immunity,*18:573-581.
107. Karlsson, M.C.I., Guinamard, R., Bolland, S., Steinman, R.M. and **Ravetch, J.V**. (2003) Macrophages control the retention and trafficking of B lymphocytes in the splenic marginal zone. *J. Exp. Med*. 198:333-340. PMC2194070
108. Zhang, Z., Zhang, M., **Ravetch, J.V**., Goldman, C. and Waldmann, T.A. (2003) Effective therapy for a murine model of Adult T-cell Leukemia with the humanized anti-CD2 monoclonal antibody, MEDI-507. *Blood,* 102:284-288.
109. Zhang, Z., Zhang, M., Goldman, C., **Ravetch, J.V.** and Waldmann, T.A. (2003) Effective therapy for a murine model of Adult T-cell Leukemia with the humanized anti-CD52 monoclonal antibody, CAMPATH-1H. *Cancer Research,* 63:6453-6457.
110. Muhlfeld, A.S., Segerer, S., Hudkins, K. Carling, M.D., Wen, M., Farr, A.G., **Ravetch, J.V.** and Alpers, C.E. (2003) Deletion of the fcgamma receptor Iib in thymic stromal lymphopoietin transgenic mice aggravates membranoproliferative glomerulonephritis. *Am J Pathol.* 163(3):1127-1136. PMC1868251
111. Turhan, A., Jenab, P., Bruhns, P., **Ravetch, J.V**., Coller, B.S., and Frenette, P.S. (2004) Intravenous immune globulin prevents venular vaso-occlusion in sickle cell mice by inhibiting leukocyte adhesion and the interactions between sickle erythrocytes and adherent leukocytes. *Blood*, 103:2397-2400.
112. Uchida, J., Hamaguchi, Y., Oliver, J.A., **Ravetch, J.V**., Poe, J.C., Haas, K.M. and Tedder, T.F. (2004) The Innate Mononuclear Phagocyte Network Depletes B Lymphocytes Through Fc Receptor-Dependent Mechanisms During Anti-CD20 Antibody Immunotherapy. *J. Exp. Med.,*199(12):1659-1669. PMC2212805
113. Zhang, M., Zhang, Z., Garmestani, K., Goldman, C.K., **Ravetch, J.V.**, Brechbiel, M.W., Carrasquillo, J.A., and Waldmann, T.A. (2004) Activating Fc receptors are required for antitumor efficacy of the antibodies directed toward CD25 in a murine model of adult t-cell leukemia. *Cancer Res* 64:5825-5829.
114. Moll, T., Nitschke, L., Carroll, M., **Ravetch, J.V**. and Izui, S. (2004) A Critical Role for FcγRIIB in the Induction of Rheumatoid Factors. *J. Immunology,* 173:4724-4728.
115. McGaha, T., Sorrentino, B. and **Ravetch, J.V**. (2005) Restoration of tolerance in lupus by targeted inhibitory receptor expression. *Science*, 307:590-593.
116. Fukuyama, H., Nimmerjahn, F. and **Ravetch, J.V**. (2005) The inhibitory Fcγ receptor

modulates autoimmunity by limiting the accumulation of immunoglobulin G^+ anti-DNA plasma cells. *Nature Immunology*, 6:99-106.

117. Dhodapkar, K.M., Kaufman, J.L., Ehlers, M., Banerjee, D.K., Bonvini, E., Koenig, S., Steinman, R.M., **Ravetch, J.V**. and Dhodapkar, M.V. (2005) Selective blockade of inhibitory Fcγ receptor enables human dendritic cell maturation with IL-12p70 production and immunity to antibody coated tumor cells. *Proc. Natl. Acad. Sci.* 102(8):2910-2915. PMC549508
118. Olsson, M., Bruhns, P., Frazier, W.A., **Ravetch, J.V**. and Oldenborg, P-A. (2005) Platelet homeostasis is regulated by platelet expression of CD47 under normal conditions and in passive immune thrombocytopenia. *Blood,* 105(9):3577-3582. PMC1895021
119. Nimmerjahn, F., Bruhns, P., Horiuchi, K. and **Ravetch, J.V**. (2005) FcγRIV: A novel FcR with distinct IgG subclass specificity. *Immunity,* 23:41-51.
120. Boruchov, A.M., Heller, G., Concetta-Veri, M., Bonvini, E., **Ravetch, J.V**. and Young, J.W. (2005) Activating and inhibitory IgG Fc receptors mediate opposing effects on human dendritic cell function. *J. Clin. Invest.,* 115: 2914-23. PMC1201664
121. Nimmerjahn, F. and **Ravetch, J.V.** (2005) Divergent immunoglobulin G subclass activity through selective FcR binding. *Science* 310: 1510-12
122. Okazaki, T., Otaka, Y., Wang, J., Hiai, H., Takai, T., **Ravetch, J.V.** and Honjo, T. (2005) Hydronephrosis associated with antiurethelial and antinuclear autoantibodies in BALB/c-FcγR2b-/-Pdcd1-/- mice. *J. Exp. Med.* 202: 1643-8. PMC2212956
123. Yamazaki, S., Patel, M., Harper, A., Bonito, A., Fukuyama, H., Pack, M., Tarbell, K., Talmor, M.**, Ravetch, J. V.,** Inaba, K. and Steinman, R.M. (2006) Effective expansion of alloantigen-specific Foxp3+CD25+ CD4+ regulatory T cells by dendritic cells during the mixed leukocyte reaction. *Proc. Natl. Acad. Sci. USA* 103: 2758-63. PMC1413800
124. Ehlers, M., Fukuyama, H., McGaha, T., Aderem, A. and **Ravetch, J.V.** (2006) TLR9/MyD88 signaling is required for class switching to pathogenic IgG2a and 2b autoantibodies in SLE. *J. Exp. Med.* 203: 553-61. PMC2118244
125. Kaneko, Y., Nimmerjahn, F., Madaio, M. and **Ravetch, J.V.** (2006) Pathology and protection in nephrotoxic nephritis is determined by selective engagement of specific Fc receptors. *J. Exp. Med.* 203: 789-97. PMC2118246
126. Zhang, M., Yao, Z., Zhang, Z., Garmestani, K., Goldman, C.K., **Ravetch, J. V.,** Janik, J., Brechbiel, M.W. and Waldmann, T.A. (2006) Effective therapy for a murine model of human anaplastic large-cell lymphoma with the anti-CD30 monoclonal antibody HeFi-1, does not require activating Fc receptors. *Blood* 108: 705-710. PMC1895489
127. Kaneko, Y., Nimmerjahn, F. and **Ravetch, J.V.** (2006) Anti-inflammatory activity of Immunoglobulin G resulting from Fc sialylation. *Science* 313:670-673
128. Mackay, M., Stavevsky, A., Wang, T., Aranow, C., Li, M., Koenig, S., **Ravetch, J.V.** and Diamond, B. (2006) Selective dysregulation of the FcgammaRIIB receptor on memory B cells in SLE. *J. Exp. Med.* 203: 2157-64. PMC2118390
129. Maltais, L.J., Lovering, R.C., Taranin, A.V., Colonna, M., **Ravetch, J.V.**, Dalla-Favera, R., Burrows,, P.D., Cooper, M.D., and Davis, R.S. (2006) New nomenclature for Fc receptor-like molecules. *Nat Immunol* 7:431-432.
130. Dhodapkar, KM, Banerjee, D, Connolly, J, Kukreja, A, Matayeva, E, Veri, MC, **Ravetch, JV,** Steinman, RM and Dhodapkar, MV (2007) Selective blockade of the inhibitory Fc{gamma} receptor (Fc{gamma}RIIB) in human dendritic cells and monocytes induces a type I interferon response program.*J. Exp. Med.* 204:1359-69. PMC2118610
131. Nimmerjahn, F, Anthony, RM and **Ravetch, JV** (2007) Agalactosylated IgG antibodies depend on cellular Fc receptors for in vivo activity. *Proc Natl Acad Sci* U SA 104:8433-7.

PMC1895967
132. Kowalewska J, Muhlfeld AS, Hudkins KL, Yeh MM, Farr AG, **Ravetch JV**, Alpers CE.(2007) Thymic stromal lymphopoietin transgenic mice develop cryoglobulinemia and hepatitis with similarities to human hepatitis C liver disease. *Am J Pathol.* 170:981-9. PMC1864872
133. Wermeling, F., Chen, Y., Pikkarainen, T., Scheynius, A., Winqvist, O., Izui, S., **Ravetch, J. V.,** Tryggvason, K. and Karlsson, M. (2007) Class A scavenger receptors regulate tolerance against apoptotic cells, and autoantibodies against these receptors are predictive of systemic lupus. *J. Exp. Med.*, 204:, 2259-2265. PMC2118440
134. Nandakumar, K.S., Collin, M., Olsen, A., Nimmerjahn, F., Blom, A., **Ravetch, J.V.,** and Holmdahl, R. (2007) Endoglycosidase treatment abrogates IgG arthritogenicity: Importance of IgG glycosylation in arthritis. *Eur. J. Imm.* 37: 2973-2982.

135. Baudino, L., Nimmerjahn, F., Azeredo da Silveira, S., Martinez-Soria, E., Saito, T., Carroll, M., **Ravetch, J.V.**, Verbeek, J.S., and Izui, S. (2008) Differential contribution of three activating IgG Fc receptors (FcgammaRI, FcgammaRIII, and FcgammaRIV) to IgG2a- and IgG2b-induced autoimmune hemolytic anemia in mice. *J Immunol* 180:1948-1953.
136. McGaha, T.L., Karlsson, M.C., and **Ravetch, J.V.** (2008) Fc{gamma}RIIB Deficiency Leads to Autoimmunity and a Defective Response to Apoptosis in Mrl-MpJ Mice. *J Immunol* 180:5670-5679.
137. Anthony, R.M., Nimmerjahn, F., Ashline, D.J., Reinhold, V.N., Paulson, J.C. and **Ravetch, J.V.** (2008) A Recombinent IgG that Recapitulates the Anti-Inflammatory Activity of IVIG. *Science* 320:373-376. PMC2409116
138. Albert, H., Collin, M., Dudziak, D., **Ravetch, J.V.**, and Nimmerjahn, F. (2008) In vivo enzymatic modulation of IgG glycosylation inhibits autoimmune disease in an IgG subclass-dependent manner. *Proc Natl Acad Sci USA* 105:15005-15009. PMC2567483
139. Baudino, L., Nimmerjahn, F., Shinohara, Y., Furukawa, J., Petry, F., Verbeek, J.S., Nishimura, S., **Ravetch, J.V.**, and Izui, S. (2008) Impact of a three amino acid deletion in the CH2 domain of murine IgG1 on Fc-associated effector functions. *J Immunol* 181:4107-4112.
140. Schupf, N., Tang, M.X., Fukuyama, H., Manly, J., Andrews, H., Mehta, P., **Ravetch, J.**, and Mayeux, R. (2008) Peripheral Abeta subspecies as risk biomarkers of Alzheimer's disease. *Proc Natl Acad Sci USA* 105:14052-14057. PMC2544577
141. Giorgini, A., Brown, H.J., Lock, H.R., Nimmerjahn, F., **Ravetch, J.V.**, Verbeek, J.S., Sacks, S.H., and Robson, M.G. (2008) FcgammaRIII and FcgammaRIV are indispensable for acute glomerular inflammation induced by switch variant monoclonal antibodies. *J Immunol* 181:8745-52. PMC2649421
142. Anthony, R.M., Wermeling, F., Karlsson, M.C., and **Ravetch, J.V.** (2008) Identification of a receptor required for the anti-inflammatory activity of IVIG. *Proc Natl Acad Sci USA* 105: 19571-8 Nov 26 e-pub. PMC 2604916
143. Otten, M.A., van der Bij, G.J., Verbeek, S.J., Nimerjahn, F., **Ravetch, J.V.**, Beelen, R.H., van de Winkel, J.G., and van Egmond, M. (2008) Experimental antibody therapy of liver metastases reveals functional redundancy between FcgammaRI and FcgammaRIV. *J Immunol* 181:6829-36.
144. Baudino, L., Shinohara, Y., Nimmerjahn, F., Furukawa, J., Nakata, M., Martinez-Soria, E., Petry, F., **Ravetch, J.V.**, Nishimura, S., and Izui, S. (2008) Crucial role of aspartic acid at position 265 in the CH2 domain for murine IgG2a and IgG2b Fc-associated effector

functions. *J Immunol* 181:6664-9.
145. Sazinsky, S.L., Ott, R.G., Silver, N.W., Tidor, B., **Ravetch, J.V.** and Wittrup, K.D. (2008) Aglycosylated immunoglobulin G1 variants productively engage activating Fc receptors. *Proc. Natl. Acad. Sci. USA* 105:20167-72. PMC2629253
146. Delgado, M.F., Coviello, S., Monsalvo, A.C., Melendi, G.A., Hernandez, J.Z., Batalle, J.P., Diaz, L., Trento, A., Chang, H.Y., Mitzner, W., **Ravetch, J.V.,** Melero, J.A., Irusta, P.M. and Polack, F.P. (2009) Lack of antibody affinity maturation due to poor Toll-like receptor stimulation leads to enhanced respiratory syncytial virus disease. *Nat. Med.* 15: 34-41. PMC2987729
147. Scheid, J.S., Mouquet, H., Feldhahn, N., Seaman, M.S., Velinzon, K., Pietzsch, J., Ott, R.G., Anthony, R.M., Zebroski, H., Hurley, A., Phogat, A., Chakrabarti, B., Li, Y., Connors, M., Pereyra, F., Walker, B.D., Wardemann, H., Ho, D., Wyatt, R.T., Mascola, J.R, **Ravetch, J.V.**, and Nussenzweig, M.C. (2009) Broad diversity of neutralizing antibodies isolated from memory B cells in HIV infected individuals. *Nature* 458:636-40. Epub 2009 Mar 15.
148. Santiago-Raber, M.L., Amano, H., Amano, E., Baudino, L., Otani, M., Lin, Q., Nimmerjahn, F., Verbeek, J.S., **Ravetch, J.V.**, Takasaki, Y., Hirose, S., and Izui, S. (2009) Fcgamma receptor-dependent expansion of a hyperactive monocyte subset in lupus-prone mice. *Arthritis Rheum.* 60:2408-17.
149. Abboud, N., Chow, S-K, Saylor, C. **Ravetch, J. V.**, Scharff, M.D. and Casadevall, A. (2010) A requirement for FcγR in antibody-mediated bacterial toxin neutralization. *J. Exp. Med.,* 207:2395-405. PMC 2964574
150. Mouquet, H., Scheid, J.F., Zoller, J.J. Krogsgaard, M., Ott, R.G., Shukair, S., Artyomov, M.N., Pietzsch, J., Connors, M., Pereyra, F., Walker, B.D., Ho, D.D., Wilson, P.C., Seaman, M.S., Eisen, H.N., Chakraborty, A.K. Hope, T.J., **Ravetch, J. V.,** Wardemann, H.,and Nussenzweig, M.C. (2010) Polyreactivity increases the apparent affinity of anti-HIV antibodies by heteroligation. *Nature* 467:537-8.
151. Nimmerjahn, F., Lux, A., Alberg, H., Woigk, M., Lehmann, C., Dudziak, D., Smith, P., and **Ravetch, J.** (2010) FcgammaRIV deletion reveals its central role for IgG2a and IgG2b activity in vivo. *Proc. Natl. Acad. Sci. USA,* 107:19396-401. Epub 2010 Oct. 25. PMC 2984189
152. Miletic, A.V., Anzelon-Mills, A.N., Mills, D.M., Omori, S.A., Pedersen, I.M., Shin, D.M., **Ravetch, J.V.**, Bolland, S., Morse, H.C. 3rd, and Rickert, R.C. (2010) Coordinate suppression of B cell lymphoma by PTEN and SHIP phosphatases. *J. Exp. Med*, 207:2407-2420. PMC 2964567
153. Anthony, R.M., Kobayashi, T., Wermeling, F. and **Ravetch, J.V.** (2011) Intravenous Gamma Globulin Suppresses Inflammation through a Novel Th2 Pathway. *Nature*, 475:110-113. PMC Journal In Press.
154. Li, F., and **Ravetch, J.V.** (2011) Inhibitory FcγR engagement drives adjuvant and anti-tumor activities of agonistic anti-CD40 antibodies. *Science,* 333:1030-1034. PMC 3164589
155. Smith, P., DeLillo, D.J..Bournazos, S., Li, F. and **Ravetch, J.V.** (2012) A mouse model recapitulating human FcγR structural and functional diversity. *PNAS*, 109, 6181-6 published online 4/2/12. PMC Journal In Press.
156. Mattsson J, Yrlid U, Stensson A, Schön K, Karlsson MC, **Ravetch** JV, Lycke NY (2011) Complement activation and complement receptors on follicular dendritic cells are critical for the function of a targeted adjuvant. *J Immunol*. 2011 Oct 1;187(7):3641-52. Epub 2011 Aug 31.

157. Li, F. and **Ravetch, J.V.** (2012) Apoptotic and anti-tumor activity of death receptor antibodies require inhibitory Fcγ receptor engagement. *PNAS*, 109, 10966-71 published online 6/18/12. PMC Journal In Press.
158. Klein F, Halper-Stromberg A, Horwitz JA, Gruell H, Scheid JF, Bournazos S, Mouquet H, Spatz LA, Diskin R, Abadir A, Zang T, Dorner M, Billerbeck E, Labitt RN, Gaebler C, Marcovecchio PM, Incesu RB, Eisenreich TR, Bieniasz PD, Seaman MS, Bjorkman PJ, **Ravetch** JV, Ploss A, Nussenzweig MC.(2012) HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. *Nature*. 6;492(7427):118-22. Epub 2012 Oct 24.
159. Pietzsch J, Gruell H, Bournazos S, Donovan BM, Klein F, Diskin R, Seaman MS, Bjorkman PJ, **Ravetch** JV, Ploss A, Nussenzweig MC (2012) A mouse model for HIV-1 entry. *Proc Natl Acad Sci U S A*. 109(39):15859-64. Epub 2012 Sep 10.
160. Sondermann, P., Pincetic, A., Maamary, J. Lammens, K. and **Ravetch, J. V.** (2013) A general mechanism for modulating immunoglobulin effector function. *Proc. Natl, Acad. Sci. USA*, 110(24):9868-72
161. Simpson, T.R., Li, F., Montalvo-Ortiz, W, Sepulveda, M.A., Bergerhoff, K., Arce, F., Roddie, C. Henry, J.Y., Yagita, H., Wolchok, J.D., Peggs,, K.S., **Ravetch, J.V.,** Allison, J.P. and Quezada, S.A. (2013) Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 antibody therapy against melanoma *JEM*, 210(9):1695-710
162. Gruell H, Bournazos S, **Ravetch JV**, Ploss A, Nussenzweig MC, Pietzsch J. (2013) Antibody and antiretroviral pre-exposure prophylaxis prevent cervicovaginal HIV-1 infection in a transgenic mouse model. *J. Virol*. 87(15):8535-44
163. Wermeling, F., Anthony,A., Brombacher, F. and **Ravetch, J.V**. (2013) Acute inflammation primes myeloid effector cells for anti-inflammatory STAT6 signaling. *Proc. Natl. Acad. Sci. USA* 110(33):13487-91
164. Bournazos, S., Chow, S-K., Abboud, N., Casadevall, A. and **Ravetch, J.V.** (2014) Human IgG Fc domain engineering enhances anti-toxin neutralizing antibody activity. *JCI*, 124:725-9
165. Li, F. and **Ravetch, J. V.** (2013) Antitumor activities of agonistic anti-TNFR antibodies require differential FcγRIIB co-engagement *in vivo*. *PNAS*, 110:19501-6
166. DiLillo, D.J., Tan, G.S., Palese,P. and **Ravetch, J.V**. (2014) Broadly neutralizing anti-HA stalk antibodies require FcγR interactions during protection from influenza challenge in vivo, *Nat. Med*. 20:143-51
167. Li F, Smith P, **Ravetch JV**. (2014) Inhibitory Fcγ receptor is required for the maintenance of tolerance through distinct mechanisms. *J. Immunol*. 192:3021-8
168. Ahmed AA, Giddens J, Pincetic A, Lomino JV, **Ravetch** JV, Wang LX, Bjorkman PJ. (2014) Structural characterization of anti-inflammatory Immunoglobulin G Fc proteins. *J. Mol Biol*. 426:3166-3179
169. Halper-Stromberg A, Lu CL, Klein F, Horwitz JA, Bournazos S, Nogueira L, Eisenreich TR, Liu C, Gazumyan A, Schaefer U, Furze RC, Seaman MS, Prinjha R, Tarakhovsky A, **Ravetch** JV, Nussenzweig MC. (2014) Broadly Neutralizing Antibodies and Viral Inducers Decrease Rebound from HIV-1 Latent Reservoirs in Humanized Mice. *Cell* 158:989-999
170. Bournazos, S, Klein, F, Pietzsch, J, Seaman, M, Nussenzweig, MC and **Ravetch, JV** (2014) Broadly neutralizing anti-HIV-1 antibodies require Fc effector functions for *in vivo* activity. *Cell* 158:1243-1253
171. DeLillo, D. and **Ravetch, J.V.** (2015) Differential Fc-receptor engagement drives an anti-tumor vaccinal effect. *Cell*, 161:1035-45

172. Wang, T.T., Maamary, J., Schlesinger, S.J., Kramer, F., Palese, P. and **Ravetch, J.V.** (2015) Anti-HA Fc glycoforms determine influenza vaccine efficacy through Type II Fc receptor signaling. *Cell,* 162:160-9
173. Fiebiger, B-M., Maamary, J., Pincetic, A. and **Ravetch, J.V.** (2015) Protection in antibody and T cell mediated autoimmune diseases by anti-inflammatory IgG Fcs requires Type II FcRs. *PNAS*, 112:E2385-94.
174. Dahan, R., Sega, E., Engelhardt, J., Selby, M. Korman, A.J. and **Ravetch, J.V.** (2015) FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell*, 28(3):285-95
175. DiLillo DJ, Palese P, Wilson PC, **Ravetch** JV. (2016) Broadly neutralizing anti-influenza antibodies require Fc receptor engagement for in vivo protection. *J Clin Invest*. 2016 126:605-10
176. Lu C.L., Murakowski D.K., Bournazos S., Schoofs T., Sarkar D., Halper-Stromberg A., Horwitz J. A., Nogueira L., Golijanin J., Gazumyan A., **Ravetch J. V.**, Caskey M., Chakraborty A., Nussenzweig M.C. (2016) Enhanced clearance of HIV-1-infected cells by anti-HIV-1 broadly neutralizing antibodies *in vivo. Science*, 352:1001-4
177. Bournazos, S, Gazumyan, A, Seaman, M.S, Nussenzweig, M.C. and **Ravetch, J.V.** (2016) Bispecific anti-HIV-1 antibodies with enhanced breadth and potency. Cell, 165:1609-20
178. Dahan R, Barnhart BC, Li F, Yamniuk AP, Korman AJ, **Ravetch** JV. (2016) Therapeutic Activity of Agonistic, Human Anti-CD40 Monoclonal Antibodies Requires Selective FcγR Engagement. *Cancer Cell*, 29:820-31
179. Georgoudaki AM, Prokopec KE, Boura VF, Hellqvist E, Sohn S, Östling J, Dahan R, Harris RA, Rantalainen M, Klevebring D, Sund M, Brage SE, Fuxe J, Rolny C, Li F, **Ravetch** JV, Karlsson MC. (2016) Reprogramming Tumor-Associated Macrophages by Antibody Targeting Inhibits Cancer Progression and Metastasis. *Cell Rep*. 15:2000-11
180. Wang, T., Sewatanon, J., Memoli, M., Wammert, J., Bournazos, S., Bhaumkik, S., Pinsky, B., Chokephaibulkit,K., Onlamoon, N., Pattanapanyasat, K., Taubenberger, J., Ahmed, R. and **Ravetch, J.V.,** (2017) Anti-dengue antibodies enhanced for FcRIIIA binding determine disease severity. *Science,* 355: 395-398
181. Li T, DiLillo DJ, Bournazos S, Giddens JP, **Ravetch** JV, Wang LX (2017) Modulating IgG effector function by Fc glycan engineering. *Proc Natl Acad Sci U S A*. 114(13):3485-3490.
182. Maamary J, Wang TT, Tan GS, Palese P, **Ravetch** JV. (2017) Increasing the breadth and potency of response to the seasonal influenza virus vaccine by immune complex immunization. *Proc Natl Acad Sci* U S A. 114(38):10172-10177.
183. Chen TF, Sazinsky SL, Houde D, DiLillo DJ, Bird J, Li KK, Cheng GT, Qiu H, Engen JR, **Ravetch** JV, Wittrup KD. (2017) Engineering Aglycosylated IgG Variants with Wild-Type or Improved Binding Affinity to Human Fc Gamma RIIA and Fc Gamma RIIIAs.. *J Mol Biol.* 2017 429:2528-2541.
184. Raz A, Serrano A, Lawson C, Thaker M, Alston T, Bournazos S, **Ravetch** JV, Fischetti VA. (2017) Lysibodies are IgG Fc fusions with lysin binding domains targeting *Staphylococcus aureus* wall carbohydrates for effective phagocytosis. *Proc Natl Acad Sci* U S A. 114:4781-4786
185. Knorr DA, Dahan R, **Ravetch** JV. (2018) Toxicity of an Fc-engineered anti-CD40 antibody is abrogated by intratumoral injection and results in durable antitumor immunity. Proc Natl Acad Sci U S A.

186. Zhang M, Wen B, Anton OM, Yao Z, Dubois S, Ju W, Sato N, DiLillo DJ, Bamford RN, **Ravetch** JV, Waldmann TA. IL-15 enhanced antibody-dependent cellular cytotoxicity mediated by NK cells and macrophages. Proc Natl Acad Sci U S A. 2018;115
187. Giddens JP, Lomino JV, DiLillo DJ, **Ravetch** JV, Wang LX. Site-selective chemoenzymatic glycoengineering of Fab and Fc glycans of a therapeutic antibody. Proc Natl Acad Sci U S A. 2018 115:12023-12027
188. Pradier L, Blanchard-Brégeon V, Bohme A, Debeir T, Menager J, Benoit P, Barneoud P, Taupin V, Bertrand P, Dugay P, Cameron B, Shi Y, Naimi S, Duchesne M, Gagnaire M, Weeden T, Travaline T, Reczek D, Khiroug L, Slaoui M, Brunel P, Fukuyama H, **Ravetch** J, Canton T, Cohen C. SAR228810: an antibody for protofibrillar amyloid β peptide designed to reduce the risk of amyloid-related imaging abnormalities (ARIA). Alzheimers Res Ther. 2018 Nov 28;10(1):117. doi: 10.1186/s13195-018-0447-y.
189. Weitzenfeld P, Bournazos S, **Ravetch** JV. Antibodies targeting sialyl Lewis A mediate tumor clearance through distinct effector pathways. J Clin Invest. 2019 Sep 3;129(9):3952-3962. doi: 10.1172/JCI128437.
190. Bournazos S, DiLillo DJ, Goff AJ, Glass PJ, **Ravetch** JV. Differential requirements for FcγR engagement by protective antibodies against Ebola virus. Proc Natl Acad Sci U S A. 2019 Sep 4. pii: 201911842. doi: 10.1073/pnas.1911842116. [Epub ahead of print]
191. Van Rompay KKA, Coffey LL, Kapoor T, et al. A combination of two human monoclonal antibodies limits fetal damage by Zika virus in macaques. *Proc Natl Acad Sci U S A*. 2020;117(14):7981-7989. doi:10.1073/pnas.2000414117
192. Borghi S, Bournazos S, Thulin NK, et al. FcRn, but not FcγRs, drives maternal-fetal transplacental transport of human IgG antibodies. *Proc Natl Acad Sci U S A*. 2020;117(23):12943-12951. doi:10.1073/pnas.2004325117
193. Glasgow A, Glasgow J, Limonta D, et al. Engineered ACE2 receptor traps potently neutralize SARS-CoV-2. Engineered ACE2 receptor traps potently neutralize SARS-CoV-2. Proc Natl Acad Sci U S A. 2020 Oct 22:202016093. doi: 10.1073/pnas.2016093117.
194. Bournazos S, Corti D, Virgin HW, **Ravetch** JV. Fc-optimized antibodies elicit CD8 immunity to viral respiratory infection. Nature. 2020 Oct 8. doi: 10.1038/s41586-020-2838-z. PMID: 33032297
195. Schäfer A, Muecksch F, Lorenzi JCC, Leist SR, Cipolla M, Bournazos S, Schmidt F, Gazumyan A, Baric RS, Robbiani DF, Hatziioannou T, **Ravetch** JV, Bieniasz PD, Nussenzweig MC, Sheahan TP. Antibody potency, effector function and combinations in protection from SARS-CoV-2 infection *in vivo*. J Exp Med. 2021 Mar 1;218(3):e20201993. doi: 10.1084/jem.20201993. PMID: 33211088
196. Eisinger S, Sarhan D, Boura VF, Ibarlucea-Benitez I, Tyystjärvi S, Oliynyk G, Arsenian-Henriksson M, Lane D, Wikström SL, Kiessling R, Virgilio T, Gonzalez SF, Kaczynska D, Kanatani S, Daskalaki E, Wheelock CE, Sedimbi S, Chambers BJ, **Ravetch JV**, Karlsson MCI. Targeting a scavenger receptor on tumor-associated macrophages activates tumor cell killing by natural killer cells. Proc Natl Acad Sci U S A. 2020 Dec 15;117(50):32005-32016. doi: 10.1073/pnas.2015343117. Epub 2020 Nov 23. PMID: 33229588; PMCID: PMC7750482.
197. La Fleur L, Botling J, He F, Pelicano C, Zhou C, He C, Palano G, Mezheyeuski A, Micke P, **Ravetch JV**, Karlsson MCI, Sarhan D. Targeting MARCO and IL37R on Immunosuppressive Macrophages in Lung Cancer Blocks Regulatory T Cells and Supports Cytotoxic Lymphocyte Function. Cancer Res. 2021 Feb 15;81(4):956-967. doi: 10.1158/0008-5472.CAN-20-1885. Epub 2020 Dec 8. PMID: 33293426.

198. Nimmerjahn F, **Ravetch JV**. Four keys to unlock IgG. J Exp Med. 2021 Mar 1;218(3):e20201753. doi: 10.1084/jem.20201753. PMID: 33600555; PMCID: PMC7888349.
199. Garris CS, Wong JL, **Ravetch JV**, Knorr DA. Dendritic cell targeting with Fc-enhanced CD40 antibody agonists induces durable antitumor immunity in humanized mouse models of bladder cancer. Sci Transl Med. 2021 Sci Transl Med. PMID: 34011627
200. Li C, Chong G, Zong G, Knorr DA, Bournazos S, Aytenfisu AH, Henry GK, **Ravetch JV**, MacKerell AD Jr, Wang LX. Site-Selective Chemoenzymatic Modification on the Core Fucose of an Antibody Enhances Its Fcγ Receptor Affinity and ADCC Activity. J Am Chem Soc. 2021 JACS
201. Bournazos S, Vo HTM, Duong V, Auerswald H, Ly S, Sakuntabhai A, Dussart P, Cantaert T, **Ravetch JV**. Antibody fucosylation predicts disease severity in secondary dengue infection. Science. 2021 Jun 4;372(6546):1102-1105. doi: 10.1126/science.abc7303. PMID: 34083490
202. Ibarlucea-Benitez I, Weitzenfeld P, Smith P, **Ravetch JV**. Siglecs-7/9 function as inhibitory immune checkpoints in vivo and can be targeted to enhance therapeutic antitumor immunity. Proc Natl Acad Sci U S A. 2021 Jun 29;118(26):e2107424118. doi: 10.1073/pnas.2107424118. PMID: 34155121
203. Ou C, Li C, Zhang R, Yang Q, Zong G, Dai Y, Francis RL, Bournazos S, **Ravetch JV**, Wang LX. One-Pot Conversion of Free Sialoglycans to Functionalized Glycan Oxazolines and Efficient Synthesis of Homogeneous Antibody-Drug Conjugates through Site-Specific Chemoenzymatic Glycan Remodeling. Bioconjug Chem. 2021 Aug 18;32(8):1888-1897. doi: 10.1021/acs.bioconjchem.1c00314. Epub 2021 Aug 5. PMID: 34351736
204. Yamin R, Jones A, Hoffmann HH, Kao K, Francis R, Sheahan T, Baric R, Rice C, **Ravetch, JV** and Bournazos S. Fc-engineered antibody therapeutics with improved efficacy against COVID-19. Nature (2021) 599, 465-470
205. Gupta A, Smith P, Bournazos S, **Ravetch JV**. A novel mouse strain optimized for chronic human antibody administration. Proc Natl Acad Sci U S A. 2022
206. Herati RS, Knorr DA, Vella LA, Silva LV, Chilukuri L, Apostolidis SA, Huang AC, Muselman A,Manne S, Kuthuru O, Staupe RP, Adamski SA, Kannan S, Kurupati RK, Ertl HCJ, Wong JL, Bournazos S, McGettigan S, Schuchter LM, Kotecha RR, Funt SA, Voss MH, Motzer RJ, Lee CH, Bajorin DF, Mitchell TC, **Ravetch JV**, Wherry EJ. PD-1 directed immunotherapy alters Tfh and humoral immune responses to seasonal influenza vaccine. Nat Immunol. 2022 Aug;23(8):1183-1192.
207. Kao KS, Gupta A, Zong G, Li C, Kerschbaumer I, Borghi S, Achkar JM, Bournazos S, Wang LX, **Ravetch JV**. Synthetic nanobodies as tools to distinguish IgG Fc glycoforms. Proc Natl Acad Sci U S A. 2022 Nov 29;119(48).

208. Gupta A, Kao KS, Yamin R, Oren DA, Goldgur Y, Du J, Lollar P, Sundberg EJ, Ravetch JV. Mechanism of glycoform specificity and in vivo protection by an anti-afucosylated IgG nanobody. Nat Commun. 2023 May 18;14(1):2853.
209. Osorio JC, Smith P, Knorr DA, Ravetch JV. The Antitumor Activities of Anti-CD47 Antibodies Require Fc-FcγR interactions. Cancer Cell 2023, 41:2051-2065
210. Yamin R, Kao KS, MacDonald MR, Cantaert T, Rice CM, Ravetch JV, Bournazos S. Human FcγRIIIa activation on splenic macrophages drives dengue pathogenesis in mice. Nat Microbiol. 2023 Aug;8(8):1468-1479
211. Wong JL, Smith P, Angulo-Lozano J, Ranti D, Bochner BH, Sfakianos JP, Horowitz A, Ravetch JV, Knorr DA. IL-15 synergizes with CD40 agonist antibodies to induce durable immunity against bladder cancer. Proc Natl Acad Sci U S A. 2023, 120:
212. Liu Y, Chen T, Zhu Y, Furey A, Lowary TL, Chan J, Bournazos S, Ravetch JV, Achkar JM. Features and protective efficacy of human mAbs targeting Mycobacterium tuberculosis arabinomannan. JCI Insight. 2023, in press
213. Knorr K, Rahman J, Erickson C, Wang E, Monetti M, Li Z, Ortiz-Pacheco J, Jones A, Lu SX, Stanley RF, Baez M, Fox N, Castro C, Marino AE, Jiang C, Penson A, Hogg SJ, Mi X, Nakajima H, Kunimoto H, Nishimura K, Inoue D, Greenbaum B, Knorr D, Ravetch J, Abdel-Wahab O. Systematic evaluation of AML-associated antigens identifies anti-U5 SNRNP200 therapeutic antibodies for the treatment of acute myeloid leukemia. Nat Cancer. 2023 , 4:1675-1692
214. Edgar JE, Trezise S, Anthony RM, Krammer F, Palese P, Ravetch JV, Bournazos S. Antibodies elicited in humans upon chimeric hemagglutinin-based influenza virus vaccination confer FcγR-dependent protection in vivo. Proc Natl Acad Sci U S A. 2023, 120:
215. Knorr D, Blanchard, L. Leidner R, Jensen S, Meng R, Jones A, Ballesteros-Merino C, Bell RB, Baez M, Sprott D, Bifulco C, Piening B, Dahan R, Fox BA, Ravetch J. FcyRIIB is a novel immune checkpoint in the tumor microenvironment limiting activity of Treg-targeting antibodies. Cancer Immunology Research 2024, 12:322-333
216. Osario, J, Smith, P, Knorr, D, Ravetch J., The anti-tumor activites of CD47 antibodies require Fc-FcR interactions (2023) Cancer Cell 41:2051-2065

Chapters and Reviews

1. Korsmeyer, S.J., Hieter, P., **Ravetch, J.V.,** Poplack, D., Leder, P. and Waldmann, T.A. Pattern of immunoglobulin gene arrangements in human lymphocytic leukemias. In: Leukemia Markers (Knapp, W., ed.) 1981; Academic Press, London.
2. **Ravetch, J.V.**, Kirsch, I.R., Siebenlist, U. and Leder, P. Multiple somatic recombination events generate heavy chain immunoglobulin genes. In: Mechanism of Lymphocyte Activation, Proceedings of the 14th Leucocyte Culture Conference (Resch, K. and Kirschner, E., eds.) 1981; Elsevier/North Holland Press, Amsterdam.
3. Leder, P., Hieter, P., Hollis, G., Kirsch, I.R., Leder, P., Nau, M. and **Ravetch, J.V.** (1982) The new image of the mammalian genome. In: Perspectives on Genes and the Molecular Biology of Cancer (Robberson, D.L., Saunders, G.F., ed.) Raven Press.
4. Kirsch, I.R., **Ravetch, J.V.**, Hieter, P.A., Korsmeyer, S.J., Waldmann, T.A. and Leder, P. (1982) Genetic rearrangements in the humoral immune system. In: Current Concepts in Human Immunology and Cancer Immunomodulations (Serrou, B., ed.) Elsevier Biomedical Press B.V.
5. Waldmann, T.A., Korsmeyer, S.J., Hieter, P.A., **Ravetch, J.V.**, Arnold, A. and Leder, P. (1983) Immunoglobulin gene rearrangements in human lymphocytic leukemia. In: Recombinant DNA Applications to Human Disease, Banbury Report 14 (Caskey, C.T. and White, R.L., ed.) Cold Spring Harbor Press, N.Y.
6. **Ravetch, J.V.**, Young, J. and Poste, G. (1985) Molecular genetic strategies for the

development of anti-malarial vaccines. *Biotechnology* 3:729-740.

7. Perkins, M., and **Ravetch, J.V.** (1985) Interaction of *Plasmodium falciparum* merozoite proteins with the erythrocyte surface. In: Vaccines, Cold Spring Harbor Laboratory Press, N.Y.
8. **Ravetch, J.V.** and Pologe, L.G. (1988) Molecular genetic strategies for parasite survival in *P. falciparum* malaria. In: Immunization (Root, Warren, Griffiss and Sande, eds.) Churchill Livingstone, Inc., New York, N.Y.
9. **Ravetch, J.V.** (1989) Chromosomal polymorphisms and gene expression in *Plasmodium falciparum*. *Exp. Parasitol.* 68:121-125.
10. **Ravetch, J.V.** and Anderson, C. (1989) Molecular diversity of FcγRs in Fc receptors and the action of antibodies chapter VI, ed. H. Metzger (American Society of Microbiology, Washington, D.C.).
11. **Ravetch, J.V.** and Kinet, J-P. (1991) Fc receptors. In: Annual Review of Immunology 9:457-92.
12. **Ravetch, J.V.** and Colton, H. (1992) Section editor: Innate Immunity in *Current Opinion in Immunology*, 4:1.
13. Lanzer, M., Wertheimer, S., de Bruin, D., and **Ravetch, J.** (1993) Plasmodium: Control of gene expression in malaria parasites. *Exp. Parasitol*. 77:121-128.
14. Lanzer, M., de Bruin, D., Wertheimer, S., and **Ravetch, J.V.** (1994) Organization of chromosomes in *Plasmodium falciparum:* A model for generating karyotypic diversity. *Parasitology Today,* 10:114-117.
15. Brooks, D. and **Ravetch, J.V.** (1994) Fc Receptor Signalling. In: Mechanisms of Lymphocyte Activation and Immune Regulation V, (Gupta, S., De Franco, A., Paul, W. and Perlmutter, R., ed.) Plenum Publishing, N.Y.
16. **Ravetch, J.V**. (1994) Atopy and Fc receptors: mutation is the message? *Nature Genetics,*

17. **Ravetch, J.V**. (1994) Fc Receptors: Rubor Redux. *Cell,* 78:553-560.
18. **Ravetch, J.V**. and Margulies, D.H. (1994) New tricks for old molecules. *Nature* 372:323-324.
19. **Ravetch, J.V**. and Colton, H. (1995) Section editor: Innate Immunity in *Current Opinion in Immunology,* 7:1-3.
20. **Ravetch, J.V**. (1997) Fc receptors. *Current Opinion in Immunology,* 9:121-125.
21. Vora, K.A., **Ravetch, J.V.** and Manser, T. (1997) Maturation of the B cell response in genetically altered mice. In: Developmental Immunology.
22. **Ravetch, J.V.** and Clynes, R.A. (1998) Divergent roles for Fc receptors and complement *in vivo*. In: Annual Review of Immunology, 16:421-32.
23. Bolland, S. and **Ravetch, J.V**. (1999) Inhibitory pathways triggered by ITIM-containing receptors. *Advances in Immunology,* 72:149-177.
24. **Ravetch, J.V.** and Lanier, L.L. (2000) Immune Inhibitory Receptors. *Science,* 290:84-89.
25. **Ravetch, J.V.** and Bolland, S. (2001) IgG Fc Receptors. In: Annual Review of Immunology, 19:275-90.
26. **Ravetch, J**.V. (2002) A full complement of receptors in immune complex diseases. *J. Clin. Invest*. 110:1759-1761.
27. **Ravetch, J.V**. (2003) Fc Receptors. In Fundamental Immunology, 5th edition, W. M. Paul, editor.
28. Steinman, R.M., Hawiger, D., Liu, K. Bonifaz, L., Bonnyay, D., Mahnke, K., Iyoda, T., **Ravetch, J**., Dhodapkar, M., Inaba, K. and Nussenzweig, M. (2003) In: *Ann. N.Y. Acad. Sci.* 987:15-25.
29. **Ravetch, J.V.** and Carroll, M.C. (2004) Fc and Complement Receptors. In: Molecular Biology of B cells. ed. T. Honjo, F. Alt and M. Neuberger, chapter 18, pages 275-289.
30. Nimmerjahn, F. and **Ravetch, J.V.** (2006) Fcgamma receptors: old friends and new family members. *Immunity* 24: 19-28
31. Ehlers, M. and **Ravetch, J.V.** (2006) Opposing effects of Toll-like receptor stimulation induce autoimmunity or tolerance. *Trends Immunol.* 28: 74-9.
32. Nimmerjahn, F. and **Ravetch, J.V.** (2007) The anti-inflammatory activity of IgG: the intravenous IgG paradox. *J. Exp. Med.,* 204: 11-15. PMC2118416
33. **Ravetch, J.V.** and Nimmerjahn, F. (2007) Fc Receptors. In *Fundamental Immunology*, chapter 22, 6th edition, W. M. Paul, editor.
34. Nimmerjahn, F. and **Ravetch, J.V.** (2007) Fc-receptors as regulators of immunity. *Adv Immunol* 96:179-204.
35. **Ravetch, J.V.** and Nussenzweig, MC (2007) Killing some to make way for others. *Nat Immunol*. 8:337-9
36. Nimmerjahn, F. and **Ravetch, J.V.** (2007) Antibodies, Fc receptors and cancer. *Curr Opin Immunol*.19:239-45
37. **Ravetch, J.V.** and Aderem, A. (2007) Phagocytic cells. *Immunol. Rev.* 219: 5-7
38. Nimmerjahn, F. and **Ravetch, J.V.** (2008) Anti-Inflammatory Actions of Intravenous Immunoglobulin. *Annu Rev Immunol* 26:513-533.
39. Nimmerjahn, F. and **Ravetch, J.V.** (2008) Fcgamma receptors as regulators of immune responses. *Nat Rev Immunol* 8:34-47.
40. Nimmerjahn, F. and **Ravetch, J.V.** (2008) Analyzing antibody-Fc-receptor interactions. *Methods Mol Biol* 415:151-162.
41. Nimmerjahn, F. and **Ravetch, J.V.** (2008) Fc Receptors. In *How the Immune System Recognizes Self and Nonself: Immunoreceptors and Their Signaling*, chapter 6, D. Kitamura, editor.

42. **Ravetch, J. V.** (2010) In vivo veritas: the surprising roles of Fc receptors in immunity. *Nature Immunology* 11:183
43. Anthony, R.M. and **Ravetch, J. V.** (2010) A novel role for the IgG Fc glycan: the anti-inflammatory activity of sialylated IgG Fcs. *J. Clin. Immunol.* 30: Suppl 1:S9-14
44. Nimmerjahn, F. and **Ravetch, J. V.** (2010) Antibody-mediated modulation of immune responses. *Immunol. Rev.* 236:265
45. Nimmerjahn, F. and **Ravetch, J. V.** (2010) FcgammaRs in Health and Disease. *Curr. Top. Microbiol. Immunol*
46. Anthony, R. M., Wermeling, F., and **Ravetch, J.** (2012) Novel roles for the IgG Fc glycan. In: *Ann. N.Y. Acad. Sci.* 1253:170-180
47. Li F, **Ravetch** JV. (2012) A general requirement for FcγRIIB co-engagement of agonistic anti-TNFR antibodies. Cell Cycle. 15;11(18):3343-4. Epub 2012 Aug 23.
48. Nimmerjahn F, **Ravetch** JV. (2012) Translating basic mechanisms of IgG effector activity into next generation cancer therapies. Cancer Immun. 12:13. Epub 2012 May 1.
49. Pincetic A, Bournazos S, DiLillo DJ, Maamary J, Wang TT, Dahan R, Fiebiger BM, **Ravetch** JV. (2014) Type I and type II Fc receptors regulate innate and adaptive immunity. Nat Immunol. 2014 Jul 21;15(8):707-716.
50. Bournazos, S., DiLillo, D. and **Ravetch, J.V.** (2014) Humanized mice to study FcR function. Curr Top Microbiol Immunol. 382:237-48.
51. Wang, TT and **Ravetch, J. V.** (2015) Immune complexes: not just an innocent bystander in chronic viral infection. Immunity. 42:213-5.
52. DiLillo DJ, **Ravetch** JV.(2015) Fc receptor interactions regulate both cytotoxic and immunomodulatory therapeutic antibody effector functions. Cancer Immunol. 3:704-13
53. Bournazos S, DiLillo DJ, **Ravetch** JV. (2015) The role of Fc-FcR interactions in IgG-mediated microbial neutralization. J Exp Med. 212(9):1361-9.
54. Bournazos S, **Ravetch** JV. (2015) Fc receptors pathways during active and passive immunization. Immunol Rev. 268:88-103
55. Bournazos S, Wang TT, **Ravetch** JV. (2016) The Role and Function of Fcγ Receptors on Myeloid Cells. Microbiol Spectr. 24(6).
56. Bournazos S, **Ravetch** JV. (2017) Anti-retroviral antibody FcγR-mediated effector functions. Immunol Rev. 275(1):285-295
57. Bournazos S, **Ravetch** JV. (2017) Attenuated Vaccines for Augmented Immunity. Cell Host Microbe. 21(3):314-315
58. Bournazos S, **Ravetch** JV. (2017) Fcγ Receptor Function and the Design of Vaccination Strategies. Immunity. 47:224-233.
59. Bournazos S, **Ravetch** JV. (2017) Diversification of IgG effector functions. Int Immunol. 29(7):303-310
60. Bournazos S, Wang TT, Dahan R, Maamary J, **Ravetch** JV. (2017) Signaling by Antibodies: Recent Progress Annu Rev Immunol. 35:285-311.
61. Wang TT, Bournazos S, Ravetch JV. Immunological responses to influenza vaccination: lessons for improving vaccine efficacy. *Curr Opin Immunol*. 2018;53:124-129. doi:10.1016/j.coi.2018.04.026
62. Knorr DA, Ravetch JV. Immunotherapy and Hyperprogression: Unwanted Outcomes, Unclear Mechanism. *Clin Cancer Res*. 2019;25(3):904-906. doi:10.1158/1078-0432.CCR-18-3144
63. Wang TT, Ravetch JV. Functional diversification of IgGs through Fc glycosylation. *J Clin Invest*. 2019;129(9):3492-3498. doi:10.1172/JCI130029

64. Bournazos S, Gupta A, Ravetch JV. The role of IgG Fc receptors in antibody-dependent enhancement [published online ahead of print, 2020 Aug 11]. *Nat Rev Immunol*. 2020;1-11. doi:10.1038/s41577-020-00410-0