UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00042
U.S. Patent No. 12,037,618

Declaration of Dr. Garnett Kelsoe

Table of Contents

I. Introductory Matters.....1

A. My Background and Qualifications 1

B. Compensation.....3

C. Materials I Considered in Formulating My Opinions.....4

II. Principles and Assumptions I Have Been Instructed to Apply.....4

A. Relevant timeframe. 4

B. Person of Ordinary Skill in the Art ("POSA").....4

C. Relevant patent documents.....5

D. "Modified PH20 Polypeptide" 6

III. Summary of My Opinions.....7

IV. Background Scientific Principles 10

A. The adaptive immune response directs the immune system at foreign antigen. 11

B. Immune tolerance mediated by B and T cells prevents autoimmunity. 14

C. Not all antigens are equally immunogenic.....18

D. Antibody binding specificity is only part of the equation necessary for therapeutic efficacy. 23

E. The circulating (systemic) and mucosal immune systems are compartmentalized but not impervious to one another.....26

V. A POSA Would Not Have Found the Use of Modified PH20 Polypeptides as Contraceptive Vaccines to Be Credible Based Upon Available Empirical Evidence. 30

A. A POSA would not have thought PH20 to be useful as a contraceptive vaccine in males. 31

B. A POSA would not have thought PH20 to be a useful antigen to include in a contraceptive vaccine, even in females. 33

C. Experimental evidence published by Halozyme after the relevant timeframe confirms expectations derived from earlier experiments. .45

VI. A POSA Could Not Have Known Which Modified PH20 Polypeptides Could Cause Infertility Without Making and Testing Each One.....50

A. A POSA could not have known which of the many modified PH20 polypeptides could elicit a relevant polyclonal response against native PH20, whether in humans or other mammals. 51

1. A POSA would not have predicted the nature of the polyclonal response based on sequence identity alone. 53

2. A POSA would not have expected that all modified PH20 polypeptides could cause a relevant polyclonal immune response against native human PH20. 57

3. A POSA would not have expected misfolded modified PH20 polypeptides to cause the production of polyclonal antibodies capable of therapeutically relevant binding to native human PH20.....62

4. A POSA would not have expected a modified human PH20 polypeptide to cause a relevant polyclonal response against native PH20 in non-human mammals.....68

B. A POSA would not have expected modified PH20 polypeptides to be useful as immunocontraceptive vaccines based on theoretical binding in humans and other mammals.....71

C. A POSA would not have expected adjuvants, boosters, and other helpful molecules to overcome the problems of a poor immunogen..80

VII. A POSA Would Have Needed to Make and Test Numerous Anti-PH20 Monoclonal Antibodies in Order to Find Ones That Could Be Useful for Contraception.....82

VIII. Conclusion 85

Appendix A - Exhibit List 87

Appendix B – CV.....93

I. Introductory Matters

A. My Background and Qualifications

1. My educational background, professional history, and other relevant qualifications are summarized below. I attach to this Declaration my curriculum vitae (Appendix B), which provides a full and accurate description of my educational background, professional experience, appointments, honors and awards, student trainees, and publications.

2. I received my Doctor of Science, a degree equivalent to a Ph.D. in a scientific field, in Immunology in 1979 from Harvard University for research involving the mechanisms of the humoral immune response and the interactions between lymphocytes (idiotypic and anti-idiotypic) that impact immune regulation, using animal modeling and antibody titer and specific binding analyses. I completed postdoctoral training as a research fellow at the University of Cologne Institute for Genetics, where I continued work in idiotypic regulation of the immune system. I received two Master of Science degrees in Tropical Public Health from Harvard University in 1975 and in Zoology from Southern Methodist University in 1974. The Harvard M.Sc. focused on parasitology and the SMU Masters Thesis described spermatogenesis in the cestode, *Hymenolepis diminuta*. I received my Bachelor of Science degree in Biology from Southern Methodist University in 1972.

3. I currently serve as James B. Duke Distinguished Professor of Immunology, Associate Professor of Surgical Sciences, and Senior Fellow of the Duke Center for the Study of Aging and Human Development, all at Duke University School of Medicine. I am also a member of the Duke Autoimmunity Center of Excellence, the Collaboration for AIDS Vaccine Discovery, and the CHAVI-ID Scientific Leadership Group. From 2006 to 2012, I served as Associate Director of the Bill & Melinda Gates Foundation Duke Vaccine Antibody Consortium. From 1999 to 2006, I served as Director of Graduate Studies in Immunology at Duke University School of Medicine.

4. Prior to my appointment at Duke, I served as Director of the University of Maryland Immunology Group from 1994 to 1995 and as Professor of Immunology from 1994 to 1998. Throughout my career, I have taught and supervised courses in immunology, microbiology, immunogenetics, and pathogenesis. I have supervised a large number of doctoral and postdoctoral researchers working in lymphocyte development, immune regulation, immune tolerance, and vaccine development.

5. I have over 45 years of research experience in microbiology and immunology. My laboratory has investigated the genetic and cellular mechanisms that shape immune responses, including detailed studies of immune tolerance, autoimmunity, vaccine development, antigen affinity, the structure/function

relationship of epitopes and antibodies, and B lymphocyte diversification and regulation, using techniques such as recombinant antibody generation, multiple sequence alignments, and structural analysis of point mutations. My work has addressed diverse biological systems, including studies of immune responses to self- and non-self-antigens in human and non-human models for the purpose of vaccine development.

6. I have received the Norman L. Letvin Scholar Award from the Duke CHAV-ID Consortium (2018) and the Duke CHAVD Scholar Award from the NIH CHAVD Consortia (2020) for contributions to the development of an effective HIV-1 vaccine. I have authored over 200 peer-reviewed scientific publications in the areas of immunology, immune tolerance, and vaccine design. A complete list of my publications is included in Appendix B. I have also served as Deputy Editor for The Journal of Immunology and the Journal of Clinical Investigation, as well as a peer reviewer for leading scientific journals, including *Nature*, *Science*, and *Immunity*.

B. Compensation

7. For my work on this matter, I am being compensated for my time at the rate of $700 per hour. My compensation is not dependent in any way on the contents of this Declaration, the substance of any further opinions or testimony that I may provide, or the ultimate outcome of this matter.

C. Materials I Considered in Formulating My Opinions

8. My opinions are based on my education, research, and experience as an immunologist, as well as investigation and analysis I have conducted of relevant materials. I relied upon my familiarity with the scientific literature in my field and have further reviewed a number of publications in developing my analysis. A list of the publications cited in this Declaration is provided in Appendix A.

II. Principles and Assumptions I Have Been Instructed to Apply

A. Relevant timeframe.

9. I have been asked by counsel to provide my opinions from the perspective of a person having ordinary skill in the art before December 30, 2011. I have also been asked to consider that perspective as of December 28, 2012. My opinions in this Declaration do not differ between December 30, 2011 and December 28, 2012 because there were no developments in the field of protein structure or immune response prediction in that timeframe that would have changed any of my opinions.

B. Person of Ordinary Skill in the Art ("POSA").

10. I have been instructed by counsel to apply the following definition of a person having ordinary skill in the art (or, "POSA"): a person who would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry,

biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques and tools used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).

11. In the context of my experience as an immunologist, I have experience with factors influencing antibody and antigen structure and interaction, and use of biological assays and tools to characterize the function and binding capabilities of these types of proteins. Accordingly, for the questions I've been asked to address regarding immunological applications of "modified PH20 polypeptides," as defined below, I had at least the relevant qualifications of a POSA by December 2011 and provide my opinions from that perspective.

C. Relevant patent documents.

12. I was asked by counsel to assess certain issues associated with U.S. Patent No. 12,037,618, referred to here as the '618 Patent (EX1001). In connection with that review, I also examined U.S. Patent Application No. 13/694,731 (the '731 Application) (EX1026).

13. It is my understanding that a patent disclosure includes a written description known as the specification, which is often accompanied by drawings

and sequence listings. These sequence listings set forth nucleotide or amino acid sequences, identified by an assigned sequence identification number (for example, SEQ ID NO: 3). I further understand that a patent concludes with claims, which set forth and define the scope of the invention.

14. I have reviewed relevant disclosures of the ’618 Patent and the ’731 Application specifications, along with a comparison of their respective specifications (EX1045). Based on my review, the specifications are substantively identical with respect to the aspects relevant to my opinion. Because the disclosures in the two patent documents are the same, I refer to them collectively in this declaration as the “common disclosure.” I cite to the specification of U.S. Patent Application No. 13/694,731, filed December 28, 2012, in referring to the common disclosure.

D. “Modified PH20 Polypeptide”

15. I understand that the ’618 Patent at issue in these proceedings concerns “modified PH20 polypeptides” with certain required characteristics. I have been asked to develop my opinions based upon the following understanding of “modified PH20 polypeptides” provided by counsel: polypeptides comprising an amino acid sequence that is at least 91% identical to the amino acid sequence of any one of SEQ ID NO: 3, 7, and 32-66 in the ’618 Patent, and includes, at least, a modification at position 309.

16. I understand and have been instructed that the recited sequences of SEQ ID NO: 3, 7, and 32-66 are forms of human PH20. I have also been instructed that amino acid modifications in "modified PH20 polypeptides" can be amino acid replacement(s), deletion(s), and/or insertion(s). Based on the understanding of the term provided by counsel, I also assume that such "modified PH20 polypeptides" can include folded proteins with tertiary structures resembling the native human PH20, as well as polypeptides that misfold and/or become insoluble due to factors such as denaturation, aggregation, and instability. Further, I assume such "modified PH20 polypeptides" include ones that retain enzymatic activity and ones that are inactive.

III. Summary of My Opinions

17. I have been asked to consider the opinion of Halozyme's expert, Dr. Cherr, that a POSA in the relevant timeframe would have expected that "any of the modified PH20 polypeptides would be useful as contraceptive vaccines in female mammals (including humans),"[1] and that "polyclonal antibodies generated in female mammals (including humans) in response to any of the modified PH20 polypeptides… (appropriately administered as vaccines) would cause

[1] EX2072 (Cherr Dec.), ¶ 12; *see also id.* ¶ 56, 62.

contraception by binding to sperm PH20 polypeptide in the female reproductive tract."[2] I disagree with Dr. Cherr.

18. As I explain in Section V, viewing the available experimental evidence together as a POSA would have done in the relevant timeframe in 2011-2012, I disagree with Dr. Cherr because a POSA would have concluded that PH20 is not a useful antigen to include in an immunocontraceptive vaccine. And because there was reason to doubt the usefulness of species-appropriate PH20 as an antigen to induce infertility, there would certainly have been even greater reason to doubt the usefulness of modified PH20 polypeptides (which are essentially mutated forms of human PH20) as antigens in immunocontraceptive vaccines in humans and other mammals, especially absent experimental evidence testing such mutated forms in contraceptive vaccine applications.

19. As I explain in Section VI.B–C, I disagree with Dr. Cherr that any of the modified PH20 polypeptides, whether or not properly administered, would have been expected to cause contraception in female humans and other mammals. A POSA would have expected that achieving infertility requires more than simply eliciting just any polyclonal antibody response. A POSA could not have predicted

---

[2] EX2072 (Cherr Dec.), ¶ 43.

which of the many possible modified PH20 polypeptides could elicit the right kind of antibody response against relevant targets on native PH20 sufficient to cause contraception without empirical testing. Administration methods and other techniques to magnify the immune response suggested by Dr. Cherr and Dr. Moon would not have overcome the problems of a poor antigen.

20. I have been asked to consider the opinion of Halozyme's expert, Dr. Moon, that a POSA in the relevant timeframe would have expected 1) that "polyclonal antibodies would be generated in a human female against any of the modified PH20 polypeptides" and that "such polyclonal antibodies would bind to the wild-type human PH20 polypeptide,"[3] and 2) that polyclonal antibodies against "any of the modified PH20 polypeptides" could be generated in "a female mammal (such as chimpanzee, Rhesus monkey, Cynomolgus monkey, cow, mouse, rat, rabbit, guinea pig, red fox, gibbon, marmoset, and orangutan" "and that such antibodies would bind to the wild-type PH20 polypeptide."[4] I disagree with Dr. Moon.

21. As I explain in Section VI.A., a POSA could not have known which

---

[3] EX2074 (Moon Dec.) ¶ 47.

[4] EX2074 (Moon Dec.) ¶ 59.

of the many possible modified PH20 polypeptides could elicit a quality polyclonal antibody response against relevant epitopes for contraception in native PH20 (human or non-human) without empirical testing. A POSA could not have predicted cross-reactivity based upon sequence identity alone. In humans, a POSA would have expected immunodominance and immune tolerance to play a role in skewing any polyclonal response toward non-native epitopes on a modified PH20 polypeptide, even assuming a properly folded modified PH20 polypeptide with tertiary structure approximating those found in the native protein. A POSA would not have expected any quality polyclonal antibody response from misfolded modified PH20 polypeptides used as antigens. Finally, a POSA would not have expected quality polyclonal antibody responses against PH20 native to other species from modified PH20 polypeptides, again because sequence identity alone could not predict the outcome and published research regarding cross-reactivity of anti-PH20 antibodies across species confirmed this.

IV. Background Scientific Principles

22. The immune system is the body's defense against foreign pathogens. To work effectively, the immune system must be able to distinguish between molecules that belong in the body ("self") and those that do not belong ("non-self"). This ability to distinguish between self and non-self and to marshal effective immune responses to non-self molecules only is a critical aspect of physiological

adaptive immune responses.

A. The adaptive immune response directs the immune system at foreign antigen.

23. The adaptive immune response is carried out by white blood cells called lymphocytes that are divided into two broad classes: B cells, which are the source for antibody responses, and T cells, which support B-cell responses to protein antigens and carry out cell-mediated, effector immune responses.

24. In antibody responses, B cells with antigen receptors that bind antigen are activated to proliferate and subsequently differentiate to secrete antibodies specific for the activating antigen. An antigen is defined as any substance that can bind to a specific antibody and elicit a response from the adaptive immune system.[5] An antigen can have multiple sites to which distinct antibody molecules bind, each such site being an antigenic determinant or "epitope."[6] The body generates millions of unique B cells, each with a different antibody-like structure called a B-cell antigen receptor (BCR) displayed on its surface. BCR are generated by a unique process of physiologic genomic rearrangements that assemble discrete gene segments into functional BCRs through a pairing of unique heavy (H) and

---

[5] EX1170 (Janeway 2012), 7.

[6] EX1170 (Janeway 2012), 21.

light (L) chain rearrangements.[7] The genetic diversity inherent in this process enables the generation of over 10^8 clonally distributed, unique BCR.[8] This collection of receptors is known as the B cell repertoire.

25. Each BCR in the repertoire can recognize a distinct antigenic B-cell epitope. B-cell epitopes must be on the surface of an antigen in order to be accessible to and recognized by a BCR. The vast majority of B-cell epitopes are conformational, rather than linear.[9] Conformational B-cell epitopes have a particular three-dimensional shape on the surface formed by the folding of the protein antigen to bring amino acid residues, often ones that are distant and discontinuous, together to form a unique shape for immune targeting. Antibody binding sites are also three-dimensional, and when a cognate antibody binds to its conformational epitope, they form a highly specific interaction much like a lock and key. Binding of these conformational epitopes typically has both greater specificity and affinity compared to binding of linear epitopes.[10] An immune

---

[7] EX1170 (Janeway 2012), 21.

[8] EX1170 (Janeway 2012), 21.

[9] EX1171 (Yang 2009), 78 ("B cell epitopes contain both continuous (~10%) and discontinuous (~90%) epitopes….").

[10] EX1184 (Laver 1990), 553 ("[A]ll determinants recognized by antibodies are conformational in that antibodies will bind with measurable affinity only to those molecules presenting the right conformation; "discontinuous" is a

response against any particular antigen is polyclonal, meaning a diverse mixture of activated B cells, each specific for a discrete epitope present on the antigen secrete antibodies identically specific for the same epitope.

26. Cell-mediated immune responses are driven by activated T cells that either directly attack foreign antigen presented to them on the surface of a host cell or signal other components of the immune system to attack the foreign molecule. T cells also play a critical role in inducing most protective and durable antibody responses and are required for immunological memory.[11] As with B cells, T cells display T-cell receptors (TCR) that are also assembled through genomic rearrangement and association of TCR subunits (α- and β-chains) to form a diverse T cell repertoire. Unlike the BCR, the TCR does not recognize native protein antigens but rather peptide fragments from protein antigens that are non-covalently associated with class I or -II major histocompatibility complex (MHC) molecules. The $CD4^+$ T cells necessary for robust and persistent antibody responses to protein

---

more accurate description of nonlinear epitopes since they are assembled from residues from several different portions of the polypeptide chain"); 555 ("It should be stressed that the residues proposed to contribute most of the binding energy are not arranged in a linear sequence but are scattered over the epitope surface; in no sense can they be considered equivalent to unfoldons identified with antisera against short peptides.").

[11] EX1170 (Janeway 2012), 13–14, 191–192.

antigens have TCR specific for peptides associated with class II MHC.[12]

27. For both B and T cells, a significant fraction of the (approximately) random association of gene segments and polypeptides to form the B and T cell repertoires will result in BCR or TCR that recognize epitopes on self-antigen. Absent self-tolerance, which is described below, these autoreactive B and T cells would attack healthy endogenous tissues and cells, causing autoimmune disease.

B. Immune tolerance mediated by B and T cells prevents autoimmunity.

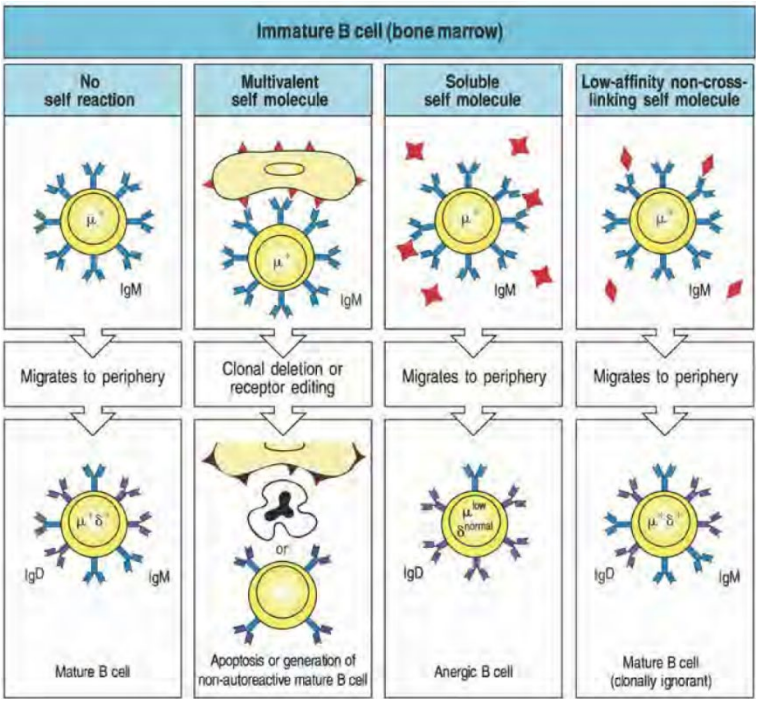
28. Immune tolerance is the physiological process whereby BCR and TCR are purged of reactivity to self-antigens. There are several ways in which tolerization occurs.

29. The tolerization of B cells occurs during maturation and is governed by two major checkpoints. The first major tolerance checkpoint occurs at the site of lymphopoiesis in bone marrow. There, B cells reactive with self-antigens either 1) die by apoptosis (clonal deletion), 2) change BCR specificity by secondary L-chain gene rearrangements (so-called receptor editing) or migrate to the periphery but 3) become permanently unresponsive to an antigen, or 4) remain incapable of

---

[12] EX1170 (Janeway 2012), 56–64.

sensing or responding to a self-antigen (immunological ignorance).[13]



(EX1170 (Janeway 2012), 85 Figure 8.12). This first tolerance checkpoint is responsible for the removal of cells such as those bearing polyreactive BCR or ones reactive with RNA and DNA polymers.[14]

30. The second major checkpoint occurs in the periphery, after the immature B cells are released from the bone marrow.[15] In the periphery, "new

---

[13] EX1172 (Bolland 2008), 667–668; EX1170 (Janeway 2012), 85 Figure 8.12, 82–87, 191–192.

[14] EX1172 (Bolland 2008), 668–669; EX1170 (Janeway 2012), 82–87.

[15] EX1172 (Bolland 2008), 668; EX1170 (Janeway 2012), 87.

emigrant" B cell maturation is regulated by T-cell help.[16] Those new emigrant B cells that become activated by self-antigen migrate to T cell zones of secondary lymphoid tissues.

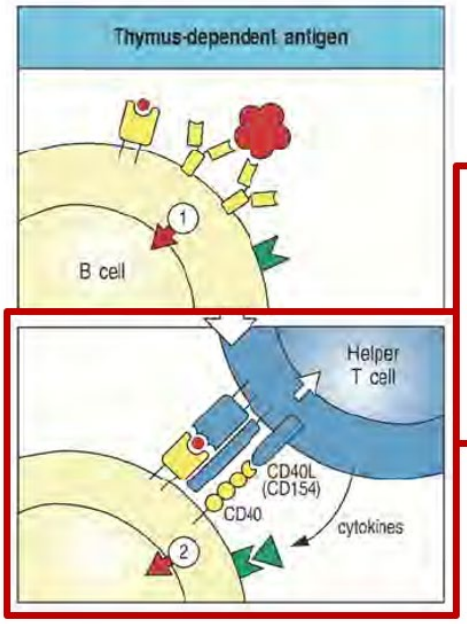


Fig. 10.2 A second signal is required for B-cell activation by either thymus-dependent or thymus-independent antigens. The first signal (indicated as 1 in the figure) required for B-cell activation is delivered through its antigen receptor (top panel). For thymus-dependent antigens, the second signal (indicated as 2) is delivered by a helper T cell that recognizes degraded fragments of the antigen as peptides bound to MHC class II molecules on the B-cell surface (center panel); the interaction between CD40 ligand (CD40L, also called CD154) on the T cell and CD40 on the B cell contributes an essential part of this second signal. For thymus-independent antigens, a second signal can be delivered along with the antigen itself, through Toll-like receptors that recognize antigen-associated TLR ligands, such as bacterial lipopolysaccharide (LPS) or bacterial DNA (bottom panel).

(EX1170 (Janeway 2012), 133 Figure 10.2.). Those that receive survival signals from $CD4^+$ helper T cells survive and mature. Without survival signals from helper T cells, the auto-reactive emigrant B cells die by apoptosis.[17]

31. One of the main mechanisms of T-cell tolerance is mediated by self-

[16] EX1172 (Bolland 2008), 668.

[17] EX1170 (Janeway 2012), 86, 133 Figure 10.2.

peptide-MHC complexes through a process called clonal deletion.[18] Another significant mechanism of tolerance in the thymus, where T cells are made, is mediated by a gene that encodes a potent transcriptional regulator called autoimmune regulator (AIRE).[19] AIRE was discovered in connection with a systemic autoimmune disease, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), associated with a monogenic cause. Mutations in AIRE that disabled its capacity for transcriptional activation resulted in autoimmunity to many self-antigens, *i.e.*, APECED.[20] The mechanism of AIRE in self-tolerance was soon after clarified in mice made deficient for the orthologous AIRE gene.[21] AIRE regulates autoimmunity by promoting promiscuous gene expression (PGE), a process by which medullary thymic epithelial cells (mTECs) express genes that are not normally expressed in the thymus.[22] This, in turn, allows mTECs to express a variety of peripheral self-antigens from other body parts ectopically in the thymus to tolerize T cells. AIRE-deficient thymic medullary

---

[18] EX1170 (Janeway 2012), 108–110.

[19] EX1170 (Janeway 2012), 109–110, 256.

[20] EX1170 (Janeway 2012), 110, 256.

[21] EX1173 (Anderson 2002); EX1170 (Janeway 2012), 256.

[22] EX1173 (Anderson 2002), 1399-1400; EX1170 (Janeway 2012), 110.

epithelial cells showed a specific reduction in ectopic expression of genes encoding peripheral antigens.[23] This observation was highly significant in understanding how central tolerance in the thymus extended to genes only expressed in distal tissues or during organismal maturation. Through this mechanism, T cells are tolerized to a panoply of peptides encoded in the genome, regardless of the location in which they are expressed and regardless of when they may be activated.[24]

32. T-cell tolerance suppresses production or expansion of antibody-producing B cell populations that recognize epitopes on native, self-protein. Incomplete T-cell tolerance, thus, has the potential to lead to autoimmune antibody production by B cells. Together, the processes of T- and B-cell self-tolerance create significant barriers for eliciting robust antibody responses to self-proteins—that is precisely their physiological role.

C. Not all antigens are equally immunogenic.

33. An immunogen is a substance that can elicit an immune response—*i.e.* it is immunogenic. By the relevant timeframe, it was well known that while all

---

[23] EX1173 (Anderson 2002), 1399-1400.

[24] EX1173 (Anderson 2002), 1397; EX1170 (Janeway 2012), 255–256.

immunogens are antigens, not all antigens are immunogens.[25] This distinction is significant with respect to self-antigens, which are normally not immunogens due to immune tolerance, as explained above in Section IV.B.

34. In addition to tolerance, it was well known that other factors influence the immunogenicity of an antigen, including its size, dosage, route of administration, composition, form, adjuvants, and interaction with host major histocompatibility complex (MHC).[26] As Dr. Moon confirmed during his deposition, the table below provides known immunological trends for how these factors influence the immunogenicity of protein antigens.[27]

---

[25] EX1170 (Janeway 2012), 310.

[26] EX1170 (Janeway 2012), 311–315.

[27] EX1170 (Janeway 2012), 312, Figure A.2.; EX1132 (Moon Dep.), 198:16–201:1 (*e.g.*, "Q: The table is describing proteins that are in particulate form to be -- to have increased immunogenicity relative to proteins that are soluble. Is that right? A: In general, particulate form of antigens are known to be more immunogenic than soluble proteins.").

Factors that influence the immunogenicity of proteins		
Parameter	Increased immunogenicity	Decreased immunogenicity
Size	Large	Small (MW<2500)
Dose	Intermediate	High or low
Route	Subcutaneous > intraperitoneal > intravenous or intragastric	
Composition	Complex	Simple
Form	Particulate	Soluble
	Denatured	Native
Similarity to self protein	Multiple differences	Few differences
Adjuvants	Slow release	Rapid release
	Bacteria	No bacteria
Interaction with host MHC	Effective	Ineffective

(EX1170 (Janeway 2012), 312, Figure A.2.) By the relevant timeframe, it was known that "[a]ntigens injected subcutaneously generally elicit the strongest responses, most probably because the antigen is taken up by Langerhans cells in the skin and efficiently presented in local lymph nodes, and so this is the method most commonly used when the object of the experiment is to elicit specific antibodies or T cells against a given antigen."[28] In contrast, the introduction of antigens into the respiratory or gastrointestinal tracts were primarily used to study allergy, though "[p]rotein antigens that enter the body through the respiratory

[28] EX1170 (Janeway 2012), Appendix I, 313.

epithelium tend to elicit allergic responses, for reasons that are not clear."[29]

35. While any given antigen will have numerous epitopes, the epitopes are not all equally immunogenic. A core principle of immunology is immunodominance, in which the immune response to a complex antigen is focused disproportionately on a few specific epitopes.[30] Immunodominance has been observed, for example, in influenza, where hemagglutinin structures vary from year to year due to immune selection in human populations.[31] This selection is focused on the hemagglutinin receptor binding site that binds to sialylated membrane proteins to initiate virus entry. Most antibodies elicited in human populations bind this immunodominant region of the hemagglutinin, halting infection.[32] This region then becomes selected for mutations that permit cell entry

---

[29] EX1170 (Janeway 2012), Appendix I, 313.

[30] *See* EX1174 (Yewdell 1999), 52 ("These findings echoed prior reports that T_{CD4+} responses to proteins frequently focused on one or a few peptides, termed immunodominant determinants (7).").

[31] EX1175 (Popova 2012), Abstract, ("H3N2 influenza viruses have now circulated in the human population for 43 years since the pandemic of 1968, accumulating sequence changes in the hemagglutinin (HA) and neuraminidase (NA) that are believed to be predominantly due to selection for escape from antibodies."), 7–8.

[32] EX1175 (Popova 2012), Abstract ("We find that most individuals, after vaccination in seasons 2006–07 and/or 2008–09, showed dominance of antigenic site B recognition over antigenic site A."), 7–8.

but resist antibody binding.[33] In contrast, the lower, virus-proximal region of hemagglutinin changes little, in part because the lower, "stem", hemagglutinin epitopes are less immunogenic.[34]

36. It was also known that the most dominant epitopes do not necessarily correspond to the most effective neutralizing ones.[35] For example, HIV-1 gp120 contains five variable loops that are highly immunogenic but also undergo constant genetic variation, which mutates out the ability of antibodies generated from a prior encounter to bind to them again.[36] Subdominant epitopes are also recognized in HIV-1 vaccinology and thought to be the consequence of several factors,

---

[33] EX1175 (Popova 2012), 8 ("In 2008 there was clear predominance of antibodies against site B in the population, predictive of the site B change K158N that was later seen in the Perth16/09 and Victoria/361/11 epidemic strains.").

[34] EX1179 (Dormitzer 2011), 171 ("Broadly neutralizing anti-stem antibodies can be elicited by immunization, but they seem to make up a generally small proportion of the elicited repertoire, but a proportion that varies between individuals, suggesting that the stem epitope is poorly immunogenic (67).").

[35] EX1176 (Gershoni 2007), 147 ("One thing that is certain is that the most dominant epitopes do not necessarily correspond to the most effective neutralizing ones. In fact, natural selection pressure tends to drive occlusion of the most neutralizing epitopes of the pathogen.").

[36] EX1176 (Gershoni 2007), 147 ("For example, the five variable loops of HIV-1 gp120 are highly immunogenic but, because of their ever changing nature, allow the swarm of HIV to evade immune surveillance by constantly mutating out of the binding capacity of the antibodies produced after first encounters.").

including location and similarity to self-antigens.[37]

37. The basis for epitopic immunodominance is unclear but likely associated with: 1) accessibility to the antigen-receptors on B cells; 2) the frequency of naïve B cells expressing cognate antigen-receptors and; 3) the availability of T-cell help for those B cells reactive to particular epitopes.[38] In the relevant 2011-2012 timeframe, and today, dominant and subdominant B-cell epitopes would have to be determined empirically.

D. Antibody binding specificity is only part of the equation necessary for therapeutic efficacy.

38. By the relevant timeframe, it was well understood that "[t]he most important characteristics of an antibody response are the specificity, quantity, affinity, and isotype (or class), of the antibodies produced."[39]

39. Specificity refers to an antibody's ability to distinguish an immunogen from other antigens. However, even a highly specific polyclonal response is not always efficacious because the ability to bind an immunogen is, alone, insufficient.

---

[37] EX1177 (Rolland 2007), 1, 5–6 ("These findings illustrate how numerous factors can intersect to establish an immunodominance hierarchy and show that high similarity to the host proteome hampers peptide immune reactivity.").

[38] EX1178 (Nelson 1994), 252.

[39] EX1170 (Janeway 2012), Appendix I, 315.

Not all epitopes on the same protein are equivalent with regard to potential therapeutic activity. Common examples are found in the epitopes on virus "entry" molecules (*e.g.*, influenza, hemagglutinin; SARS-CoV-2, spike; HIV-1, envelope). These large and complex molecules have many epitopes but only a subset bound by antibody halt virus entry into cells.[40] Thus, the location on an antigen that an antibody binds matters.

40. Beyond occlusion of functional sites on the antigen, the biological functions (effector functions) triggered by an antibody binding to its cognate antigen are determined by its isotype.[41] Different isotypes are capable of generating different effector functions such as the activation of macrophages or natural killer cells, or cell lysis through complement fixation. Predominant IgA responses, typically associated with mucosal surfaces (*e.g.*, gut, nasopharynx, reproductive tracts) rely less on effector functions and more on direct

---

[40] EX1175 (Popova 2012), 3. *See e.g.*, EX1179 (Dormitzer 2011), 171 ("Broadly neutralizing anti-stem antibodies can be elicited by immunization, but they seem to make up a generally small proportion of the elicited repertoire, but a proportion that varies between individuals, suggesting that the stem epitope is poorly immunogenic (67).").

[41] EX1170 (Janeway 2012), 315.

neutralization.[42] The isotypic composition also determines the persistence of an antibody, which in turn affects the amount available at the pertinent site.[43]

41. The strength of binding (which is called "affinity" when referring to monovalent binding and "avidity" when considering the total binding strength of a multivalent antibody molecule) also matters to eliciting an effective therapeutic response.[44] That antibody binding strength is a critical factor in effective humoral immune function has been well known since the mid-1960s.[45] The greater the binding affinity or avidity, the more efficient is the antibody response at eliminating bound pathogen.[46] A certain degree of avidity is also often required to

---

[42] EX1180 (Mantis 2011), 603 ("Whereas IgG promotes killing and clearance of pathogenic bacteria through coordinated activity of complement and Fc-mediated uptake by macrophages and neutrophils, it is generally assumed that SIgA acts primarily through receptor blockade, steric hindrance, and / or immune exclusion.").

[43] EX1170 (Janeway 2012), Appendix I, 315.

[44] EX1170 (Janeway 2012), 44–45, Appendix I, 315.

[45] EX1181 (Siskind 1965), Abstract; EX1182 (Levine 1967), 652; EX1183 (Fauci 1970), 215, Abstract.

[46] EX1170 (Janeway 2012), 315 ("Finally, the strength of binding of the antibody to its antigen in terms of a single antigen binding site binding to a monovalent antigen is termed its affinity; the total binding strength of a molecule with more than one binding site is called its avidity. Binding strength is important, because the higher the affinity of the antibody for its

recruit important immune effector and other biological functions to clear the bound pathogen.[47]

E. The circulating (systemic) and mucosal immune systems are compartmentalized but not impervious to one another.

42. The immune system can be thought to have a series of anatomically distinct compartments. As relevant here, the circulating or systemic compartment refers to the adaptive immune response to antigens that have entered the tissues or spread into the blood. Another distinct compartment is the mucosal immune system, which comprises mucosal tissue found in gastrointestinal, respiratory, and reproductive organs.[48]

43. Although the systemic and mucosal immune systems are different compartments, serum antibodies can transit into mucosal surfaces via

---

antigen, the less antibody is required to eliminate the antigen, because antibodies with higher affinity will bind at lower antigen concentrations.”).

[47] EX1183 (Fauci 1970), 219 (“Recent studies correlating the avidity of antibody for its antigenic determinant with its role in biologic reactions (1, 8, 9) raise the possibility that antibody affinity is directly related to the complement-fixing efficiency of the immune complex.”). *See also* EX1170 (Janeway 2012), 152 (“IgM molecules form pentamers with 10 antigen-binding sites, conferring higher overall avidity when binding to multivalent antigens such as bacterial capsular polysaccharides, and so compensating for the low affinity of the IgM monomers”).

[48] EX1170 (Janeway 2012), 209–210.

transudation.[49] For example, it was known by the late 1990s that "systemic immunization with sperm-specific antigens in macaques and mice…, or non-gamete antigens in a variety of species …, results in significant levels of predominantly IgG antibodies in oviductal fluids (up to 27% of those found in serum) which are derived from serum."[50]

44. Another example is Gardasil9, the current nonavalent vaccine against human papilloma virus (HPV), which is highly effective in preventing cervical, vaginal, vulvar, anal, and oropharyngeal cancers caused by specific HPV types. It is administered intramuscularly but acts across the mucosal surfaces of the human oral, reproductive, and terminal digestive tracts.[51] Protection against HPV-induced malignancies is mediated by antibody.[52]

45. A peer-reviewed article in 2012 described a human trial comparing

---

[49] EX1185 (Lu 1993), Abstract ("[R]esults suggesting that transudation of serumborne antibodies is the main source of gp 160-specific antibodies in the vaginal fluid of HIV-I-infected women.").

[50] EX2114 (Frayne 1999), 17.

[51] EX1186, (Kemp 2008), 3611 (reporting good correlation between serum anti-HPV16/18 antibody levels with the cervical secretion antibody levels).

[52] EX1186 (Kemp 2008), 3608 ("Based on several pre-clinical models, neutralizing antibodies are expected to be the primary immune mechanism for protection.").

the efficacy of sublingual (*i.e.* directed at the mucosal system) versus intramuscular (*i.e.* directed at the circulating system) administration of Gardasil4 (the previous format of the current Gardasil9 vaccine).[53] Female volunteers were either immunized via sublingual drops or by intramuscular injection. Intramuscular vaccination was more effective in generating protective serum IgG as well as cervical and vaginal IgG capable of virus neutralization.[54] Sublingual vaccination produced significantly lower serum IgG antibody (2.6% of IM vaccinees) and only about 50% of IgG antibody in cervix/vagina.[55]

46. At his deposition, Dr. Moon confirmed that the intramuscular administration of Gardisil4 resulted in a greater frequency of antibody secreting cells than the sublingual administration.[56] After reviewing the article's suggestion that these results were due to transudation of serum IgG, Dr. Moon further

---

[53] EX1120 (Huo 2012).

[54] EX1120 (Huo 2012), 5–6, Abstract ("IM antigen delivery induced or boosted HPV-specific serum IgG and pseudovirus-neutralizing antibodies, HPV-specific cervical and vaginal IgG, and elicited circulating IgG and IgA antibody secreting cells. SL antigens induced ,38-fold lower serum and ,2-fold lower cervical/vaginal IgG than IM delivery, and induced or boosted serum virus neutralizing antibody in only 3/12 subjects.").

[55] EX1120 (Huo 2012), 3–4.

[56] EX1132 (Moon Dep.), 110:1–14; EX1120 (Huo 2012), 5, Figure 2.

confirmed that "[i]n general, serum IgG can translocate to [the] reproductive tract."[57] I agree, and this would have been known to a POSA by the relevant timeframe.[58]

Page 110

Q. And so, the responses being shown are over a 20-day period with different -- with the vaccine, with different -- different formulation of the HPV16 VLP.

And, just generally, does the response seen with the intramuscular administration appear to be at or above the level of the response observed with the sublingual administration of the vaccines?

DR. KHANDURI: Objection; scope.

(Witness reading.)

A. In general, the data points associated with the intramuscular in Panel A seem to be higher than what's shown in Panel B with the sublingual route.

Q. Look at the paragraph on the right column, at the bottom of the page, that starts, "One of the potential translational advantages...."

Do you see that paragraph?

A. Yes, I see that paragraph.

Q. And there's a statement in there. It says:

...while intramuscular immunization was capable of inducing measurable virus neutralizing activity in

Page 111

cervical and/or vaginal secretions in 3/6 subjects (concomitant with high serum neutralizing titers suggesting transudation of serum IgG)....

Do you know what "transudation of serum IgG" is referring to?

A. I assume it refers to translocation from serum to cervical and/or vaginal sites, in this sentence.

Q. Okay. So that's one way antibodies in the circulation that result from a systemic immunization can get into the mucosal compartment within the reproductive tract of human females. Right?

DR. KHANDURI: Objection; form, scope.

A. In general, serum IgG can translocate to reproductive tract.

Q. If you could go to the next page, and there's a figure there, Figure 3.

And again, it's comparing the effects of immunization by the intramuscular route -- those are the three graphs on the left side -- and sublingual immunization on the right side.

And in this graph, "A" refers to the

(EX1132 (Moon Dep.), 110:1–14, 111:17–18.)

47. Similarly, HIV-1 vaccine development strategies have focused on parenteral administration even though natural transmission is across mucosal

[57] EX1132 (Moon Dep.), 111:17–18; EX1120 (Huo 2012), 5.

[58] *See*, *e.g.*, EX2114 (Frayne 1999), 17.

surfaces.[59] Thus, even in instances where the mucosal surfaces are the target for antibody response, systemic administration (via subcutaneous, intramuscular, or other forms of injection) can be more effective than mucosal administration.

V. A POSA Would Not Have Found the Use of Modified PH20 Polypeptides as Contraceptive Vaccines to Be Credible Based Upon Available Empirical Evidence.

48. In his declaration, Dr. Cherr states that "by December 28, 2012, PH20 polypeptide vaccines had been successfully used for contraception in female guinea pigs."[60] He suggests that a POSA would have expected modified PH20 polypeptides, irrespective of any required amino acid modification or additional modification(s), to be useful as contraceptive vaccines based on this guinea pig research.[61] Dr. Cherr further suggests that such expectation would not have been "undermined" by studies in other animals reporting no contraceptive effect following immunization with PH20.[62] I disagree with Dr. Cherr's conclusions.

---

[59] EX1187 (Montefiori 2012), 431–432 (detailing the results of three HIV vaccines that made it to phase III clinical trials, all of which were administered parenterally).

[60] EX2072 (Cherr Dec.), ¶ 35 (citing EX2119 (Myles 1984); EX1022 (Primakoff 1997); EX2010 (Primakoff 1988); EX1023 (Tung 1997)).

[61] EX2072 (Cherr Dec.), ¶ 44; EX1129 (Cherr Dep.), 40:23-42:19.

[62] EX2072 (Cherr Dec.), ¶ 44.

A. A POSA would not have thought PH20 to be useful as a contraceptive vaccine in males.

49. I begin by observing that neither Dr. Cherr nor Dr. Moon have provided an opinion regarding the usefulness of modified PH20 polypeptides as contraceptive vaccines in males. The common disclosure suggests that modified PH20 polypeptides, including "inactive enzymes," can be used as vaccines in contraceptive applications. This suggestion appears to apply to both males and females.[63]

> Modified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications. PH20 is present in the male reproductive tract, and is expressed in both the testis and epididymis and is present in sperm. PH20 plays a role in fertilization by facilitating entry of the sperm through the cumulus layer surrounding the unfertilized egg. PH20 also is able to bind to hyaluronic acid (HA) on the zona pellucida during early phases of fertilization. This binding also initiates intracellular signaling that aids in the acrosome reaction. Immunization with PH20 has been show to be an effective contraceptive in male guinea pigs (Primakoff et al. (1988) *Nature* 335:543-546, Tung et al. (1997) *Biol. Reprod.* 56:1133-1141). It also has been shown to be an effective contraceptive in female guinea pigs due to the generation of anti-PH20 antibodies that prevent sperm and egg binding. In examples herein, the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2. The polypeptides can be administered directly or can be administered as a recombinant virus to deliver the antigen.

(EX1026 ('731 Application), 226.). The common disclosure references studies by the Primakoff group and states that immunization with PH20 was an "effective"

[63] EX1026 ('731 Application), 226.

contraceptive in both male guinea pigs as well as female guinea pigs.[64]

50. One of the cited papers, Tung 1997 (EX1023), reports that the majority of male guinea pigs developed experimental autoimmune orchitis (EAO), and that the observed infertility was due to the absence of sperm in the epididymis.[65] A POSA would thus have understood that the cause of infertility in male guinea pigs arising from immunization with PH20 was likely due to autoimmune inflammation rather than specific antibody-mediated responses against native PH20. Consequently, although the common disclosure points to effective contraception in male guinea pigs, suggesting that modified PH20 polypeptides can be used as contraceptive vaccines in males, a POSA would have had reason to question that conclusion.

51. Dr. Cherr confirmed that a POSA would not consider modified PH20 polypeptides to be viable contraceptive vaccines in human males.[66] I agree.

---

[64] EX1026 ('731 Application), 226.

[65] EX1023 (Tung 1997), 1133. *See also* EX2114 (Frayne 1999), 2 ("However, it has subsequently been shown that autoimmune orchitis was induced in the male guinea-pigs with the resultant infertility attributable to the absence of sperm in the epididymis (Tung et al., 1997).").

[66] EX1129 (Cherr Dep.), 38:13–23.

2 Q. (By Ms. Wang) And what is the pathogenic
3 issue you are referring to with respect to human
4 males?
5 MR. POWERS: Objection. Form. Scope.
6 THE DEPONENT: So in -- you referred to
7 the guinea pig males that were injected with PH20.
8 And there was epididymitis and orchitis in the
9 testes with massive inflammation. And that was
10 what was deemed to be responsible for the
11 contraceptive effect rather than any sort of
12 antibody binding to cells, per se.
13 Q. (By Ms. Wang) And you wouldn't want to
14 cause epididymitis or orchitis in humans?
15 MR. POWERS: Objection. Form.
16 THE DEPONENT: I would not.
17 Q. (By Ms. Wang) So the POSA would not
18 think that modified PH20 polypeptides would be a
19 viable contraceptive vaccine in humans?
20 MR. POWERS: Objection.
21 Q. (By Ms. Wang) Human males?
22 MR. POWERS: Form.
23 THE DEPONENT: I -- that is correct.

(EX1129 (Cherr Dep.), 38:13–23.)

B. A POSA would not have thought PH20 to be a useful antigen to include in a contraceptive vaccine, even in females.

52. Dr. Cherr stated that a modified PH20 polypeptide would need to cause close to 100 percent infertility to be useful as a contraceptive in humans. He also believes that a modified PH20 polypeptide would need to cause similar infertility to hormone contraceptives (which is typically near 100%) to be useful in nonhuman mammals.[67]

[67] EX1129 (Cherr Dep.), 57:16–58:15.

16 Q. And I am trying to understand how do you
17 define "useful"?
18 A. Yes, so -- I define "useful" -- I mean,
19 there's -- in the literature with experimental
20 animals reducing litter size, people still use the
21 term as an effective contraception. But in my
22 mind, when it comes to human biology, it needs to
23 be close to 100 percent.
24 Q. So from modified PH20 polypeptide to be a
25 useful contraceptive in humans, it would need to

1 cause 100 percent infertility?
2 MR. POWERS: Object to form.
3 THE DEPONENT: Or close to 100 percent,
4 yes.
5 Q. (By Ms. Wang) For a modified PH20
6 polypeptide to be a useful contraceptive in
7 nonhuman mammals, how much or what percentage of
8 reduction in fertility would need to be achieved?
9 MR. POWERS: Objection. Form.
10 THE DEPONENT: It would be similar
11 ideally.
12 Q. (By Ms. Wang) It would need to be 100
13 percent or close to it?
14 A. Similar to what hormone contraceptives
15 are.

(EX1129 (Cherr Dep.), 57:16–58:15.). Dr. Cherr's opinions regarding the expected usefulness of modified PH20 polypeptides are irreconcilable with this high threshold, particularly in view of the experimental evidence available by the relevant timeframe. A POSA would have viewed it as extraordinarily unlikely that every possible modified PH20 polypeptide could elicit antibody responses that would provide near-100% effective contraception. To claim otherwise flouts well-established immunological principles.

53. Dr. Cherr's opinion relies exclusively on purportedly successful contraception in guinea pigs, and he evidently disregards the studies of other groups unable to elicit a contraceptive state by immunization with species-appropriate PH20.[68] I do not agree that this would have been a POSA's approach to

[68] EX2072 (Cherr Dec.), ¶¶ 35, 44.

consideration of the available experimental evidence.

54. First, there are irregularities in the guinea pig experiments (EX2010, EX1022) that would have caused a POSA to question the contraceptive effect observed in those studies. As I already noted above, the infertility observed in male guinea pigs was likely attributable to autoimmune inflammation rather than antibody-mediated neutralization of native PH20 activity.[69] Further studies in male guinea pigs by the same group "found no correlation of infertility with a precise serum titer threshold, suggesting that additional factors are operative in determining fertility status."[70]

55. Similar irregularities between antibody titer and contraceptive effect were observed in female guinea pigs. Notably, the anti-PH20 serum antibody titer reported for infertile female guinea pigs injected with affinity purified guinea pig PH20 suggests the necessity for very high levels of serum antibody to achieve effective contraception.[71] In testing for the reversal of contraceptive effect, the researchers also observed "a fourfold decrease" (relative to initial antiserum titers)

---

[69] *See* ¶ 43 above; EX1023 (Tung 1997), 1133.

[70] EX1022 (Primakoff 1997), 1145.

[71] EX2010 (Primakoff 1988), 545, Table 2.

at six months after the initial injection.[72] But while females immunized with 10- and 20-µg doses of PH20 were fertile at six months, "the 30 µg-immunized female, with an identical titre, remained infertile (Table 2)."[73] It is unclear why the same antibody titer would have led to different results in fertility. The researchers merely concluded that "when serum titres have fallen fourfold, any individual female has a certain probability of being either fertile or infertile."[74]

56. Furthermore, the Primakoff authors used affinity purified PH20 in their experiments. Another paper published by the same group in 1988 describes their methods, which involved using three previously characterized monoclonal antibodies that "recognize at least two and probably three different epitopes on the PH-20 antigen" to capture PH20 from sperm using affinity chromatography.[75] The paper reveals that the affinity purified PH20 protein "exists in three structural forms separable on reducing SDS-PAGE: the major 64 kDa form, the lower molecular mass 56 kDa form, and the cleaved 41-48 kDa and 27 kDa forms."[76] It is

---

[72] EX2010 (Primakoff 1988), 545.

[73] EX2010 (Primakoff 1988), 545–46, Table 2.

[74] EX2010 (Primakoff 1988), 546.

[75] EX1161 (Primakoff 1988 II), 921.

[76] EX1161 (Primakoff 1988 II), 932.

not reported whether further separation of these forms was conducted before injection into guinea pigs. It is therefore possible that the Primakoff authors immunized using multiple different forms of a protein presumed to be PH20.

57. Even setting aside these irregularities, the guinea pig experiments are the only reported experimental success before the relevant timeframe. Other groups that tested recombinant PH20 in rabbits (Pomering 2002) and in mice (Hardy 2004) failed to achieve infertility *in vivo*.[77] Both groups elicited strong polyclonal antibody responses against the respective recombinant PH20 antigens used to induce them, as demonstrated through PH20-specific plasma antibody titers.[78] However, in spite of the polyclonal response, neither group achieved infertility through immunization.[79] This demonstrates that merely eliciting a polyclonal antibody response is insufficient to achieve functional neutralization of the target antigen; more is required.

58. Dr. Cherr downplays these negative results by criticizing their experimental design, and particularly the method of immunization—subcutaneous in Pomering 2002 and intraperitoneal in Hardy 2004—which failed to generate

---

[77] EX1020 (Pomering 2002); EX1019 (Hardy 2004).

[78] EX1020 (Pomering 2002), 178; EX1019 (Hardy 2004), 330.

[79] EX1020 (Pomering 2002), 180; EX1019 (Hardy 2004), 331.

sufficient anti-PH20 antibodies in the reproductive tract.[80] But the Primakoff researchers that conducted the guinea pig experiments also employed the subcutaneous injection method of immunization in both male and female guinea pigs and were able to raise significant antibody titer and reported infertility after just one injection.[81] The authors of Pomering 2002 and Hardy 2004 also hypothesized alternative explanations for the failure to achieve infertility.

59. For example, the Pomering 2002 authors suggested that the lack of effect of immunization on fertility in rabbits may be because "PH-20 is not as important for sperm-egg binding in rabbits as it is in guinea-pigs."[82] They observed that the "distribution of PH-20 is certainly different between species," and that "guinea-pig PH-20 is found predominantly on the post-acrosomal head region whilst in the rabbit it is found mainly in the acrosomal contents and the subacrosomal/perinuclear material."[83]

---

[80] EX2072 (Cherr Dec.) ¶¶ 48–50.

[81] EX2010 (Primakoff 1988), 544; EX1022 (Primakoff 1997), Abstract, 1144.

[82] EX1020 (Pomering 2002), 181.

[83] EX1020 (Pomering 2002), 181. They further observed that "[s]tudies are presently in progress to determine if immunization methods that elicit mucosal immune responses may be more effective at inducing immunocontraception." *Id.* Dr. Cherr did not identify any published results from these studies, and I am not aware of any such results.

60. PH20 was known to be not only multifunctional, but to also exist in different structural forms depending on the stage of the fertilization process.[84] PH20 on the post-acrosomal head region is a GPI-anchored membrane protein, whereas PH20 in the acrosomal contents is a soluble form lacking the GPI-anchor.[85] Dr. Cherr acknowledged that a POSA would have known that the location of sperm capacitation in guinea pigs is different from other mammals,[86] and that PH20 is expressed in a different location on guinea pig sperm compared to other mammals.[87] Thus, a POSA would have understood that there are differences across species in terms of at least PH20's importance to fertilization, location of PH20 expression, and the predominant structural form of PH20 relevant to fertilization. A POSA could not then reasonably generalize successful contraception in one species to another without knowing and accounting for these differences.

61. The Hardy 2004 authors similarly observed that the difference in reported results "could reflect more fundamental differences in the biological role

---

[84] EX1188 (Cherr 2001), Abstract, 520; EX2108 (Hunnicutt 1996), 80, 84.

[85] EX1188 (Cherr 2001), 516.

[86] EX2072 (Cherr Dec.), ¶ 53.

[87] EX1129 (Cherr Dep.), 159:2–6.

of PH20 between the two species."[88] They also suggested that the recombinant PH20 proteins used as antigens may not contain critical immunocontraceptive epitopes found in the native PH20 protein.[89] The authors tested two different vaccine formulations of murine PH20 (mPH20): direct intraperitoneal injection (a common immunization method in mice capable of generating robust antibody responses) of purified mPH20 fused to maltose-binding protein (MBP-mPH20) and a recombinant murine cytomegalo-virus expressing mPH20 (MCMV-mPH20).[90] The two formulations produced different immune responses, as summarized in Table 1.[91]

---

[88] EX1019 (Hardy 2004), 333.

[89] EX1019 (Hardy 2004), 332.

[90] EX1019 (Hardy 2004), 327.

[91] EX1019 (Hardy 2004), 330, Table 1.

Table 1 Prevalence of seropositive sera by Western blot in BALB/c mice treated with recombinant mPH20 vaccines.

Treatment	Sex	Total number of mice	Number of seropositive mice[a]		
			Sperm	GST-mPH20	Sperm + GSTmPH20
MBP	Female	10	10	0	0
MBP	Male	5	2	0	0
MBP-mPH20	Female	10	10	6	6
MBP-mPH20	Male	5	4	4	4
rMCMV-mPH20	Female	6	1	4	1
rMCMV-mPH20	Male	6	1	3	0

[a] Sera were collected 2 weeks after the final boost (MBP, MBP-mPH20) or 150 days after infection (rMCMV-mPH20). Mice were scored as seropositive if bands were visible on Western blots probed with 1:100 diluted sera.

(EX1019 (Hardy 2004), 330, Table 1.)

62. The Hardy 2004 authors attributed this difference in immune response to "differences in the structural features of the two recombinant mPH20 antigens."[92] Further, because neither formulation resulted in infertility, "[t]his again may indicate that the native mPH20 protein could contain critical immunocontraceptive B-cell epitopes that were not present in the recombinant forms."[93] The Hardy 2004 authors thus appeared to believe, consistent with the expectation of a POSA, that only some small subset of PH20 epitopes were responsible for contraception. If so, the notion that any antibody to any PH20

[92] EX1019 (Hardy 2004), 332.

[93] EX1019 (Hardy 2004), 332.

epitope would exert a contraceptive effect cannot be true. The modified PH20 polypeptides I have been asked to address in my opinion are inherently recombinant forms that may differ from the native PH20 in presentation of critical immunocontraceptive B-cell epitopes in various ways.

63. I further observe that the Hardy 2004 authors specifically noted that "the lack of contraceptive effect with mPH20 is unlikely to be due to limitations of the delivery systems."[94] The same group had earlier achieved 100% infertility of female mice with a different antigen—mZP3—using the same intraperitoneal and viral vector delivery systems.[95] Moreover, the Hardy 2004 authors tested the sera of immunized mice for specificity to PH20, but not for neutralization or blocking of PH20 function. As I explained above in Section IV.D., not all binding antibodies are equally effective at neutralizing the target antigen. That is the nature of the polyclonal response.

64. Taken together, a POSA would not have concluded with confidence, as Dr. Cherr does, that the only reason the Pomering 2002 and Hardy 2004 experiments failed was due to inadequate delivery. To the contrary, a POSA was

---

[94] EX1019 (Hardy 2004), 333.

[95] EX1019 (Hardy 2004), 333 (*citing* Lloyd 2003).

aware that serum antibodies could transude into the mucosa and that systemically administered vaccines were capable of generating significant antibody responses in the reproductive tract.[96] An equally plausible, indeed a more likely conclusion, would have been that the early success observed in guinea pigs was an outlier, potentially due to differences unique to that species or the crude nature of the antigen used. Dr. Cherr acknowledges species differences as well, but I disagree with his conclusion that the reproductive differences between species would have caused a POSA to give less consideration to the Pomering 2002 and Hardy 2004 research.[97] If anything, this should have reinforced the conclusion that the ability to use PH20 as a contraceptive vaccine is species-dependent, and that the early success reported in guinea pigs could not be generalized to other species.

65. By the relevant timeframe, PH20 had also been tested in primates (macaques) for contraceptive effect. As summarized in Martin-DeLeon 2006, the only group able to achieve infertility remained the Primakoff group and their study using affinity purified PH20 in guinea pigs.[98]

---

[96] *See* Section IV.E.

[97] *See* EX2072 (Cherr Dec.), ¶¶ 51–53.

[98] EX1189 (Martin-Deleon 2006), 119, Table 3; EX1129 (Cherr Dep.), 114:19–115:23 (Dr. Cherr confirmed he did not find any studies outside of the

Table 3
SPAM1 and Immunocontraception

Species	Immunization			Fertility	Response	Reference
	M	F	Form	Reduction		
Guinea pigs[a]	+	+	Aff. Purif.	+	(1) Caudal sperm depletion (2) Autoimmune orchitis	Primakoff et al. (1988), Tung et al. (1997)
Rabbit	+	+	rSPAM1	–	Restricted entry of IgG in reproductive tracts	Pomering et al. (2002)
Macaque	+	+	rSPAM1	–	"	Deng et al. (2002)
Mouse	+	+	rSpam1	–	"	Hardy et al. (2004)

M: male, F: female, Aff. Purif.: affinity purified, rSPAM1/Spam1: recombinant SPAM1.
[a] The guinea pig may be fundamentally different from other species in its autoimmune response.

(EX1189 (Martin-Deleon 2006), 119 Table 3.)

66. Specifically, "[i]n a primate model, Cynomolgus macaques, combinations of adjuvant and antigens derived from synthesized and recombinant proteins all produced significant immune responses in females, with circulating antibodies recognizing macaque sperm surface PH-20 (Deng et al., 2002). However, there was a lack of sterility following immunization in this model also (Deng, personal communication)."[99] This led the author to conclude that "[t]aken together, the data from non-primate and primate models (where there are no known redundant reproductive hyases) ***suggest that PH-20 is not a useful antigen for inclusion in immunocontraceptive vaccines***."[100]

67. Viewing the available experimental evidence together as a POSA

Primakoff guinea pig work where immunization with PH20 caused contraception.).

[99] EX1189 (Martin-Deleon 2006), 119.

[100] EX1189 (Martin-Deleon 2006), 119 (emphasis added).

would have done in the relevant timeframe in 2011-2012, I disagree with Dr. Cherr that a POSA would have chosen to exclusively consider the positive Primakoff results in guinea pigs while ignoring negative results in all other species. Rather, a POSA would have concluded (as set forth in Martin-Deleon 2006) that PH20 is not a generally useful antigen to include in an immunocontraceptive vaccine. Because there was reason to doubt the usefulness of species-appropriate PH20 as an antigen to induce infertility, there would certainly have been even greater reason to doubt the usefulness of modified PH20 polypeptides (which are essentially mutated forms of human PH20) as antigens in immunocontraceptive vaccines in humans and non-human mammals.

C. Experimental evidence published by Halozyme after the relevant timeframe confirms expectations derived from earlier experiments.

68. I disagree with Dr. Cherr's dismissal of both Rosengren 2015 (EX1061) and Rosengren 2018 (EX1024) because they were published after 2012.[101] Both papers were published by scientists associated with Halozyme and confirm what a POSA would have concluded before the relevant timeframe based upon available animal experimental data: that immunization with PH20, though it

[101] EX2072 (Cherr Dec.), ¶ 45.

may induce an immune response, is unlikely to establish a state of infertility. I understand that scientists associated with Halozyme have published even more experimental evidence confirming this expectation.

69. In 2022, a group of scientists with the first author Printz investigated the risk that antibodies reactive to recombinant human PH20 (rHuPH20) would interact with endogenous PH20.[102] Among other things, the scientists predicted linear B-cell epitopes on human PH20 and mapped their locations using three antibody preparations against rHuPH20 on a peptide array.[103] The three rHuPH20-reactive antibody preparations were: a mouse 3E8 monoclonal IgG1 antibody of unknown provenance, rabbit polyclonal antibody, and polyclonal human IgG. Although the mouse monoclonal antibody and rabbit polyclonal antibody bound to separate peptides from human PH20, with the rabbit polyclonal antibody binding to several such peptides, the human polyclonal IgG did not bind to ***any*** peptide.[104]

---

[102] EX1122 (Printz 2022).

[103] EX1122 (Printz 2022), 9–11.

[104] EX1122 (Printz 2022), 11.

Table III rHuPH20-Reactive Antibodies Binding to the rHuPH20 Peptide Array

rHuPH20-reactive antibody	Peptide/sequence
Monoclonal mouse IgG1	LVQQQNVQLSLTEAT
Polyclonal rabbit IgG	LNFRAPPVIPNVPFL
	EPLDMSLFSFIGSPR
	NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKD-VYKNRSIELVQQQNVQLS
	NVQLSLTEATEKAKQ
	LGKLLRPNHLWGYYLFPDCY
	VEIKRNDDLSWLWNE
	NWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCKE
	DTDAVDVCIADGVCIDAFLKPPMETEEPQIFY
Polyclonal human IgG	None

IgG, immunoglobulin G; *IgG1*, immunoglobulin G1; *rHuPH20*, recombinant human hyaluronidase PH20

(EX1122 (Printz 2022), 11 (Table III).)

70. This Printz 2022 finding is consistent with the normal consequences of immune tolerance in humans, as I have laid out in Section IV.B. above. The peptide sequences used in the array represent predicted B-cell epitopes on human PH20. Those would likely be recognized as "self" by the human immune system and activated B cells against those self-epitopes would be deleted and unable to produce antibodies against those epitopes. Consequently, the observed result: no human polyclonal IgG binding to any predicted human B-cell epitope on PH20.

71. The Printz 2022 authors also reported immunogenicity findings from clinical trials where rHuPH20 was co-administered subcutaneously with a variety of therapeutic molecules.[105] Notably, in one study of 47 subjects reporting a high

[105] EX1122 (Printz 2022), 9.

(44.7%) incidence of anti-rHuPH20 antibodies, "[n]o neutralizing antibodies were detected in any subject from this study (37)."[106] Overall, "[a]cross all studies, one patient from a completed study developed confirmed positive neutralizing antibodies, resulting in an overall incidence of 0.04% (1/2,643) in individuals exposed to rHuPH20."[107] This observation, like the B-cell epitope analysis, is consistent with immune tolerance at work, normally removing antibodies that would interfere with critical endogenous functions. Further, it is yet another example confirming that merely binding antibodies do not always block function or impair fertility.

72. Another paper from scientists associated with Halozyme published in 2024 further illustrates the point that binding to PH20 does not necessarily result in impairment of fertility.[108] Referencing the Pomering 2002 and Hardy 2004 work, the Nolan 2024 authors stated: [109]

---

[106] EX1122 (Printz 2022), 9.

[107] EX1122 (Printz 2022), 9 and Table IV; *see also* EX1061 (Rosengren 2015), Abstract.

[108] EX1190 (Nolan 2024).

[109] EX1190 (Nolan 2024), 370 (Hardy 2004 is reference 42, and Pomering 2002 is reference 43).

fertility [41]. Additionally, previous nonclinical studies attempted to achieve contraception by immunizing against PH20 across multiple animal species [42–44]. Despite the successful generation of PH20-reactive antibodies, these studies failed to demonstrate disruption of fertility or pregnancy [42–44]. As rHuPH20 is administered both in co-

(EX1190 (Nolan 2024), 370.). The Nolan 2024 authors then describe using several different animal models to evaluate the safety profile of rHuPH20 and the anti-drug antibodies (ADA) that may form against it. The scientists reported finding anti-rHuPH20 antibodies in rabbit and mouse models and that such antibodies were neutralizing with respect to both human PH20 and the PH20 endogenous to that species.[110] However, there were "no detrimental effects on fertility as measured by sperm concentration and motility, litter size, litter viability, and development."[111] Immunization of non-human mammals with human PH20 therefore did not impair fertility in those species tested.

73. Both Printz 2022 and Nolan 2024 confirm what a POSA would have recognized from the totality of evidence available before the relevant timeframe: that PH20 was unlikely to be useful as an antigen in an immunocontraceptive vaccine in humans or mammals other than guinea pigs.

---

[110] EX1190 (Nolan 2024), 372-73, 375-76 (rabbits), 374 (mice).

[111] EX1190 (Nolan 2024), 381.

VI. A POSA Could Not Have Known Which Modified PH20 Polypeptides Could Cause Infertility Without Making and Testing Each One.

74. I earlier stated that I must assume the "modified PH20 polypeptides" I have been asked to consider in my opinion can include folded proteins with tertiary structures resembling the wild-type, native human PH20, but also polypeptides that misfold and/or become insoluble due to factors such as denaturation, aggregation, and instability.[112] I am unaware of any investigation by the relevant timeframe into the structure of modified PH20 polypeptides with multiple amino acid modifications, whether any have tertiary structures resembling the native human PH20, or whether any are misfolded. I am furthermore unaware of any investigation by the relevant timeframe into epitopes presented by such modified PH20 polypeptides. Dr. Moon stated he did not investigate the structure of PH20, changes to that structure in the reproductive tracts, or published information regarding epitopes on PH20.[113] He stated that he did not identify any particular modifications on PH20 but rather pictured them in his mind.[114]

75. I am unaware of any publication or research by the relevant timeframe

---

[112] *See* Paragraph 16.

[113] EX1132 (Moon Dep.), 150:25-151:25.

[114] EX1132 (Moon Dep.), 63:19–65:21.

in which any of the modified PH20 polypeptides I have been asked to consider in my opinion were tested for the potential to elicit immunocontraceptive antibody responses, whether in humans or other mammals. Dr. Cherr confirmed he was not aware of any successful use of modified PH20 polypeptides as contraceptive vaccines in humans or other mammals.[115] He was also not aware of any publication before 2012 investigating the effect of native or modified human PH20 polypeptides and their effect on fertility in nonhuman mammals.[116]

76. I therefore understand the opinions of Drs. Cherr and Moon with respect to modified PH20 polypeptides are not founded in experimental evidence. I disagree with the conclusions of Drs. Moon and Cherr, which I find to be oversimplified and inconsistent with basic principles of immunology of which a POSA would have been aware.

A. A POSA could not have known which of the many modified PH20 polypeptides could elicit a relevant polyclonal response against native PH20, whether in humans or other mammals.

77. Dr. Moon opined that POSAs would have expected that "polyclonal antibodies would be generated in a human female against ***any*** of the modified

---

[115] EX1129 (Cherr Dep.), 101:18–102:9.

[116] EX1129 (Cherr Dep.), 104:9–20.

PH20 polypeptides" and that "such polyclonal antibodies would bind to the wild-type human PH20 polypeptide."[117] He also opined that "POSAs would have expected to generate polyclonal antibodies in a female mammal (such as chimpanzee, Rhesus monkey, Cynomolgus monkey, cow, mouse, rat, rabbit, guinea pig, red fox, gibbon, marmoset, and orangutan) against ***any*** of the modified PH20 polypeptides … and that such antibodies would bind to the wild-type PH20 polypeptide."[118] I disagree.

78. Dr. Moon's opinions are largely based upon sequence identity. I disagree that a POSA would have formed expectations based upon sequence identity, as I explain in Section VI.A.1. Even where a modified PH20 polypeptide could be made and properly folded, a POSA could not have predicted the nature of the immune response in humans to such modified polypeptides for several reasons that I address in Section VI.A.2. With respect to modified PH20 polypeptides that are misfolded, it is even less likely that a POSA could have predicted which of such polypeptides could elicit a polyclonal response capable of engaging with the native PH20. As I address in Section VI.A.3, a POSA would have more reasonably

---

[117] EX2074 (Moon Dec.) ¶ 47 (emphasis added), ¶ 57.

[118] EX2074 (Moon Dec.) ¶ 59 (emphasis added).

expected misfolded PH20 polypeptides would fail to elicit significant antibody responses to native PH20 in humans or other mammals. Finally, I disagree with and address Dr. Moon's opinions with regard to polyclonal responses in non-human mammals in Section VI.A.4.

1. A POSA would not have predicted the nature of the polyclonal response based on sequence identity alone.

79. Dr. Moon suggests that the "high degree of amino acid sequence identity (at least 91%) between the administered modified PH20 polypeptides and the wildtype human PH20 polypeptide (SEQ ID NO: 7)" would cause all modified PH20 polypeptides to elicit immune responses against native PH20 in humans, "irrespective of (1) the location of an amino acid difference on any of the administered modified PH20 polypeptides compared to the wild-type PH20 polypeptide…."[119] I disagree with Dr. Moon because a POSA would have expected the location of amino acid changes to matter to the nature of an immune response elicited by a modified PH20 polypeptide.

80. Dr. Moon seems to assume that epitopes are discrete, structural units and that changes in one epitope are not communicated to other epitopes. By the relevant timeframe, it had been reported that epitope conformation can, in certain

[119] EX2074, ¶¶ 44, 45.

instances, be sensitive to changes at distant sites.[120] In other words, changes in one location on a polypeptide could impact the conformation of distant epitopes in other locations on the polypeptide. Dr. Moon's model requires that change in one (or more) protein domains have no overall effect on protein structure, but he provided no experiment evidence supporting such a model for PH20.

81. Dr. Moon's reasoning based upon "polyclonal antibodies [that] were known to cross-react with (bind to) a polypeptide having as low as ~ 46–49% sequence identity with the polypeptide antigen that stimulated the antibody response" is also meaningless without considering the location of differences between two sequences.[121] From an immunological perspective, a POSA would have expected significant differences in response and cross-reactivity between proteins where the differences are all localized to one domain versus proteins where the differences are spread out.

82. Consider, for example, proteins with two globular domains (A and B) of roughly 250 amino acids. Saying that Protein 1 and Protein 2 have 50% sequence identity does not identify where the sequences differ. Protein 1 and

---

[120] EX1191 (McCutcheon 1993), Abstract.

[121] *See* EX2074 (Moon Dec.), ¶ 43.

Protein 2 could have identical A domains but entirely different B domains where all the 50% difference is localized. In such an example, antibodies to Protein 1 would likely bind to the A domain of Protein 2, but not elsewhere. Alternatively, Protein 3 and Protein 4 could have 50% identity where the differences are spread throughout both the A and B domains. In such an example, the epitopic similarity between Protein 3 and Protein 4 cannot be predicted without experimentation, even if both proteins retain structures suitable for expression by a mammalian cell.

83. Influenza A virus (IAV) hemagglutinins (HA) are a real-world example of why sequence identity alone does not guarantee cross-reactivity. In humans, the clustering of 13 serotypes (distinct antibody patterns) corresponds to the amino acid sequence identity between two IAV HA clusters, called Groups 1 and 2.[122] Group 1 Has (H1, H2, H5, H6, H8, H9, H11, H12, and H13) and Group 2 HAs (H3, H4, H7, and H10) exhibit different patterns of amino acid identity. In Group 1, researchers reported "the closest pair is H2 and H5 (74.1%) followed by the pairs H1-H2 (67.2%), H8-H12 (66.7%), H1-H5 (65.5%) and H9-H12 (65.1%)."[123] According to Dr. Moon's reasoning, immunization with an H1 or H2

---

[122] EX1192 (Nobusawa 1991), Abstract.

[123] EX1192 (Nobusawa 1991), 480.

antigen should readily elicit cross-reactive (and presumably, functionally effective) antibody to IAV expressing the H5 HA given their degree of identity (67.2% and 74.1%, respectively). Yet this is not the case. Whereas the current influenza quadrivalent vaccine contains both H1 and H2 protein antigens, the United States Center for Disease Control cautions that the seasonal flu vaccine will not protect against H5N1 bird flu associated with the H5 HA.[124] While this is a recent example, the principle is true of each seasonal flu vaccine and would have been known by the relevant timeframe.

84. With respect to PH20, it had been reported by the relevant timeframe that despite the "high degree of sequence identity" with murine PH-20 and human PH-20, "polyclonal antibodies against [guinea pig] PH-20 react only weakly with mouse sperm (unpublished results) or human sperm (38)."[125] The sequence identity reported at the time between murine and guinea pig PH20, and between human and guinea pig PH20, was over fifty percent.[126] A POSA would therefore have known not only that cross-reactivity could not be predicted based on sequence identity

---

[124] EX1193 (CDC on H5N1).

[125] EX2013 (Lin 1993), 10075.

[126] EX2074 (Moon Dec.), ¶ 51 (comparing wild type PH20 to rat PH20 (54.3% and 55.5%) and guinea pig (59.4% and 60.1%)); EX1150 (Chowpongpang 2004), Table 1.

alone, but also that sequence identity was not predictive of cross-reactivity in the case of PH20 specifically.

2. A POSA would not have expected that all modified PH20 polypeptides could cause a relevant polyclonal immune response against native human PH20.

85. Dr. Moon opined that all modified PH20 polypeptides would be expected to elicit a polyclonal response against native human PH20 "even if some epitopes on the modified polypeptide were changed or disrupted (*e.g.*, an epitope in the active site of PH20 polypeptide)…."[127] It is unclear what "active site" Dr. Moon was referring to, but I disagree that a POSA would have expected a quality and relevant polyclonal antibody response to modified PH20 polypeptides where the active sites relevant to fertilization were disrupted or changed.

86. By the relevant timeframe, PH20 was understood to have multiple functional domains relevant to reproduction. PH20 is a multifunctional protein.[128] It is a hyaluronidase (meaning it acts as an enzyme to break down hyaluronic acid), it serves as a receptor for hyaluronic acid (HA)-induced cell signaling, and it acts as a receptor for the zona pellucida surrounding the oocyte to facilitate sperm

---

[127] EX2074 (Moon Dec.), ¶ 44; *see also id.* ¶ 47.

[128] EX2072 (Cherr Dec.), ¶ 19; EX1188 (Cherr 2001), Abstract, 520; EX2108 (Hunnicutt 1996), 80; EX2119 (Myles 1984), 1640; EX1195 (Zhang 2003).

binding.[129] By the relevant timeframe, a POSA would have appreciated that these different functions were likely associated with different domains of PH20. For example, researchers reported that an anti-PH-20 monoclonal antibody that inhibited sperm-zona binding by approximately 90% had no effect on hyaluronidase activity.[130] Similarly, it was known that PH20 has enzyme activity at both acid and neutral pH and that "these activities appear to involve two different domains in the protein."[131] There was also evidence suggesting that PH20 undergoes structural change in this hyaluronidase domain as it transits the reproductive tract, with an endoproteolytic cleavage at the time of the acrosome reaction that may alter three-dimensional structure.[132] Finally, at least in primates, there was evidence indicating that the HA binding domain is distinct from the hyaluronidase domains.[133]

87. By the relevant timeframe, a POSA had no insights into whether vaccination with PH20 (human or otherwise) could cause contraceptive effects,

---

[129] EX1188 (Cherr 2001), 515.

[130] EX2108 (Hunnicutt 1996), Abstract, 82.

[131] EX1188 (Cherr 2001), Abstract.

[132] EX1188 (Cherr 2001), 517; EX2108 (Hunnicutt 1996), 84.

[133] EX1188 (Cherr 2001), 519.

much less how they might do so, given the lack of experimental success in animal models other than guinea pigs. A POSA would have expected that at least one, if not several, of the multiple functional domains in PH20 would need to be neutralized by antibodies in order to achieve infertility through immunocontraception in humans.[134] Introducing multiple amino acid replacements in PH20 on top of the particular modification at position 309 would have been expected to abolish one or more of these functional domains by denaturation of the native protein structure in at least some of the possible modified PH20 polypeptides. Even if some of the modified PH20 polypeptides could be made, determining which of these modified polypeptides could be made to retain appropriately folded epitopes relevant to PH20's multiple functions present on the native PH20 was an empirical exercise.[135]

88. Even assuming a modified PH20 polypeptide that, despite multiple modifications, was made into a properly folded protein with tertiary structures

---

[134] I disagree with Dr. Cherr's opinion that it does not matter where on PH20 antibodies bind, as I address further in Section VI.B. below.

[135] It is very likely that some—or perhaps many—of the possible modified PH20 polypeptides would be unable to be expressed by mammalian cells and would represent misfolded proteins that lacked the epitopes present on native PH20.

resembling the wild-type, native human PH20, a POSA would have expected immune tolerance and immunodominance to impact the nature of a polyclonal response against such a polypeptide. In short, a POSA would have expected the polyclonal response to be more likely focused on the regions of a modified PH20 polypeptide that are *different* from the native PH20.

89. As I explained in Section IV.C., not all epitopes on a protein are equally immunogenic or equally likely to cause the generation of a therapeutically useful antibody response. By extension, one cannot assume that the immune response and quantity of antibody response will be directed equivalently to all the epitopes presented by modified PH20 polypeptides.

90. Immune tolerance against self-antigen would very likely play a role in suppressing relevant antibodies against native PH20.[136] Although in humans PH20 is primarily expressed in the male testes and epididymis, it is encoded by a gene on human chromosome 7, which is present in both males and females.[137] Human females would likely be tolerized to native PH20 through central tolerance

---

[136] In this respect, I disagree with the apparent suggestions of Drs. Moon and Cherr that it is sufficient that modified PH20 polypeptides would be treated as a "foreign" antigen in females. EX2074 (Moon Dec.), ¶¶ 20-23, 42; EX2072 (Cherr Dec.), ¶ 31 (relies on Moon).

[137] EX1196 (Dunn 2005), Background, 4 Figure 2; EX1119 (Csozka 2001), 499.

regulated by AIRE, as described above in Section IV.B. (Indeed, without tolerance intercourse would regularly trigger immune responses in all females.). T-cell tolerance will (through ectopic expression by AIRE) cause to be diminished (by regulatory T cells) or eliminated those TCR that recognize native PH20. Antibody production in response to immunization with any one of the many possible modified PH20 polypeptides would consequently be limited. Perhaps non-native regions of the polypeptide—*i.e.* those portions that are modified—would escape tolerance. T-cell "help" for B cells would then be restricted to B cells presenting the non-native (*i.e.* modified) regions of the modified PH20 polypeptide that could associate with MHC II molecules.[138] Antibodies produced by these B cells would thus be heavily skewed toward the altered regions of the modified PH20 polypeptide.

91. Self-tolerance would also have been expected to play a role in the number of B cells with BCR reactive to native PH20 in the first place. For example, a 2007 study of how HIV-1 features contribute to immune recognition analyzed the extent of the similarity between HIV-1 and the human proteome.[139]

---

[138] EX1178 (Nelson 1994), 250, 252.

[139] EX1177 (Rolland 2007).

The authors found that "…high similarity to the host proteome hampers peptide immune reactivity."[140] This finding was based on an "inverse relationship" between the degree of similarity to the native and epitope recognition.[141] Based on this inverse relationship, if B cells with BCR reactive to native PH20 cells are infrequent, the more immunogenic mutated regions of a modified PH20 polypeptide are likely to dominate the immune response yielding few, if any, antibodies in the polyclonal response that bind to relevant epitopes on native human PH20.

3. A POSA would not have expected misfolded modified PH20 polypeptides to cause the production of polyclonal antibodies capable of therapeutically relevant binding to native human PH20.

92. Dr. Moon opined that all modified PH20 polypeptides would be expected to elicit a polyclonal response against native human PH20 even if "the modified PH20 polypeptide underwent a conformational change (*e.g.*, due to intentional denaturation)."[142] It is unclear what Dr. Moon considers "intentional" denaturation and whether he considered all forms of modified PH20 polypeptides

---

[140] EX1177 (Rolland 2007), 6.

[141] EX1177 (Rolland 2007), 2.

[142] EX2074 (Moon Dec.), ¶ 44; *see also id.* ¶ 47.

(as I have), which could include misfolded and/or insoluble forms, ones that can't be expressed by mammalian cells, or those that are so unstable they aggregate in solution. Regardless, I disagree with Dr. Moon, a POSA would not have expected denatured or misfolded forms of modified PH20 polypeptides to elicit a quality polyclonal response in humans.

93. I understand the modified PH20 polypeptides I've been asked to consider in my opinion can contain multiple amino acid modifications, including substitutions, insertions, and/or deletions, in addition to the required modification at position 309. At least some of the possible multiple modifications would be expected to denature the native protein structure. This sort of structural change often results in misfolded and/or insoluble proteins that cannot transit the endoplasmic reticulum (ER) and are targeted by ubiquitin for destruction in the proteosome.[143] A POSA would know methods of producing mammalian proteins in prokaryotes to bypass proteosomal degradation, but these proteins are recovered as insoluble inclusion bodies requiring (to the extent possible in view of modifications to the amino acid sequence) solubilization and refolding.[144] These

---

[143] EX1170 (Janeway 2012), 35–36; EX1197 (Hirsch 2009), Abstract, 454.

[144] EX1198 (Singh 2005), Abstract, 303 ("Inclusion bodies produced in Escherichia coli are composed of densely packed denatured protein molecules in the form of particles. Refolding of inclusion body proteins into

methods are inefficient and often produce non-native protein structures. Moreover, prokaryotic systems do not typically support glycosylation, which was known to be important to PH20 structure and function.[145] Thus, a POSA would have expected that it was highly likely that some, and perhaps a great many, of the possible modified PH20 polypeptides would be misfolded forms of the native structure, or would be unstable, causing them to unfold or denature before injection. Such forms would lack the epitopes present on native PH20, including those relevant to contraception. Immunization with such misfolded modified PH20 polypeptides would not be expected to elicit a quality polyclonal response against native PH20 because the modified antigen would be expected to have different structures from the native.

94. Dr. Moon appears to suggest that denaturing would not matter to the overall polyclonal response because of the availability of linear epitopes.[146] Again,

---

bioactive forms is cumbersome, results in poor recovery and accounts for the major cost in production of recombinant proteins from E. coli.”).

[145] EX1199 (Li 2002), Abstract, 5 (“We conclude that the hyaluronidase activity of sperm surface PH-20 is dependent on structural features established by sulfhydryl linkages, as well as glycosylation.”).

[146] EX2074 (Moon Dec.), ¶ 45 (citing EX2137 (Lipman 2005), 260 as “stating that because polyclonal antibodies ‘recognize multiple epitopes, some of which are likely to be linear” and because ‘conformational changes [in an antigen] may not influence all epitopes to the same degree,’ the ‘impact of

it is unclear whether Dr. Moon considered the unintended disruption of structure caused by modification of multiple amino acid residues (as I understand the phrase "modified PH20 polypeptides" permits), or if he was considering a more limited form of "intentional" denaturation.[147] Dr. Moon's opinion is an oversimplification. A POSA would have understood that the nature and quality of a polyclonal immune response to misfolded antigen could be significantly different and insufficient to achieve the therapeutic goal of contraception.

95. While it is true that denatured antigens or peptides representing linear epitopes can sometimes elicit protective immunity, the protection conferred by such peptides is limited due to an inability to present discontinuous (*i.e.* conformational) epitopes.[148] Dr. Moon identified one paper claiming that urea-

---

conformational change [in an antigen] is of less concern' for polyclonal antibodies").

[147] EX2074 (Moon Decl.), ¶ 44. Dr. Moon cited a paper comparing monoclonal to polyclonal antibodies, which states "[c]onformation may be altered by any number of factors, including association with other proteins, posttranslational modification, temperature, pH, salt concentration, and fixation" but does not mention changes to the amino acid sequence as a conformational change. EX2137 (Lipman 2005), 260.

[148] EX1201 (Rodriguez 2009), D92 (reporting results of peptide vaccines against foot and mouth disease virus (FMDV), noting "[t]he results of these studies suggest that peptide vaccines representing only a limited number of antigenic sites and/or T-cell epitopes of the virus are not able to induce significant protection. Furthermore, the above sites represent only

denatured antigen (ovalbumin, a non-self protein) elicited strong antibody responses in mice.[149] However, the paper describes using an enzyme-linked immunosorbent assay (ELISA) on ovalbumin-coated plates to evaluate antibody responses.[150] This type of assay was known to yield potentially erroneous results that overstate the extent of cross-reactivity between antibodies against denatured ovalbumin and native ovalbumin "due to the denaturation of native-ovalbumin on the surface of the ELISA plate."[151] Furthermore, the antigen in this study was denatured, intentionally, by chemical reduction of disulfide bonds in already-produced (*i.e.* folded) ovalbumin, and not by modification of the amino acid sequence itself.[152]

---

continuous regions of the virus capsid. However, some of the antigenic sites on the virus are discontinuous and involve different regions of a capsid protein or more than one protein.").

[149] *See* EX2074 (Moon Dec.), ¶ 23, 45, 57.

[150] EX2074, 444.

[151] EX1162 (Koch 1996), 121; EX1163 (Leder 1994) (describing methods to accurately determine cross-reactivity and describing problems of immunoassays that may give erroneous results because the native antigen is unfolded during the assay).

[152] EX2167 (Huang 2007), 444 ("CM-OVA was prepared by reduction of disulfide bonds after stirring overnight under vacuum suction with 8.0M urea and 0.2M 2-mercaptoethanol").

96. Dr. Moon's opinion also ignores the importance that affinity and avidity play in an effective immune response. A POSA would have expected that successful contraceptive antibody responses would not only have to target the appropriate PH20 domains that block conception in the female reproductive tract, but those antibodies would necessarily have to bind with sufficient avidity (binding strength) to achieve contraceptive activity. As discussed above in Section IV.D., binding specificity is only part of the equation.

97. By the relevant timeframe, it was known that "[r]elatively minor changes in antigen structure can markedly affect the strength of the interaction" with an antibody.[153] It was also known that "[w]ith respect to native protein antigens" (such as PH20), "the binding affinity of most antibodies is influenced by conformational determinants, and antibodies may not bind the same protein in a denatured state."[154] And even if an antibody cross-reacts with a similar epitope on a different antigen, the binding is "usually with less affinity."[155] Dr. Moon acknowledges that conformational changes can affect "the strength of the

---

[153] EX2137 (Lipman 2005), 260.

[154] EX2137 (Lipman 2005), 260.

[155] EX2137 (Lipman 2005), 260.

interaction" between an antigen and antibody.[156] But he otherwise ignores this key issue, which minimizes the importance of antibody affinity and avidity in its neutralizing and effector activity. A POSA would have known not to ignore this. Rather, a POSA would have expected that denatured or misfolded modified PH20 polypeptides, even if they presented linear epitopes, might well be unable to elicit a relevant and potent polyclonal antibody response against the native human PH20.

98. Finally, a POSA would have expected the issues of immunodominance and immune tolerance, as discussed above in Sections IV.B–C. and Paragraphs 85–91, to play a role in a polyclonal response to denatured or misfolded modified PH20 polypeptides as well. B cells reactive to such forms, even with limited T-cell help, would have been less likely to produce effective antibodies reactive with the native PH20 protein.

4. A POSA would not have expected a modified human PH20 polypeptide to cause a relevant polyclonal response against native PH20 in non-human mammals.

99. Dr. Moon's opinion that a POSA "would have expected to generate polyclonal antibodies in a female mammal (such as chimpanzee, Rhesus monkey, Cynomolgus monkey, cow, mouse, rat, rabbit, guinea pig, red fox, gibbon,

---

[156] EX2074 (Moon Dec.), ¶ 23.

marmoset, and orangutan) against any of the modified PH20 and that such antibodies would bind to the wild-type PH20 polypeptide" is based almost entirely on sequence identity.[157] I have explained why a POSA would not have built expectations on sequence identity alone in Section VI.A.1, and that analysis holds true with respect to the use of modified PH20 polypeptides (which are modified human polypeptides) in nonhuman mammals as well.

100. As with his analysis for humans, Dr. Moon concludes that "irrespective of (1) the location where the amino acid difference is on any of the administered modified PH20 polypeptides compared to the wild-type PH20 polypeptide introduced via sperm into the vaccinated animal, (2) whether any of the administered modified PH20 polypeptides was enzymatically active, or (3) whether the administered modified PH20 polypeptide has conformational change (*e.g.*, due to intentional denaturation), POSAs would have expected the polyclonal antibodies generated against the administered modified PH20 polypeptide to include antibodies that would bind to the wild-type PH20 polypeptide introduced via sperm into the vaccinated animals."[158]

---

[157] EX2074 (Moon Dec.), ¶ 59; *see generally* EX2074 (Moon Dec.), ¶¶ 48–56.

[158] EX2074 (Moon Dec.), ¶ 57.

101. I have addressed and explained why I disagree, and why each of these factors would have impacted a POSA's expectations regarding a human polyclonal response to any modified PH20 polypeptides in Sections VI.A.1–4 above, and that same analysis applies to nonhuman mammals as well. In addition, immune tolerance to conserved epitopes on human PH20 (which are likely to be functional epitopes) can occur in other species. For example, if immune tolerance is operative against a B cell with BCR reactive to an epitope on rabbit PH20, and that epitope is conserved in human PH20, immunizing the rabbit with human PH20 could well result in the rabbit's self-tolerance mitigating the antibody response to that shared epitope. If anything, the lower degree of sequence identity between a given modified PH20 polypeptide and native PH20 in a given species would have reduced the likelihood of a polyclonal response against the native PH20.

102. As noted above, by the relevant 2011-2012 timeframe, it had been reported that despite the "high degree of sequence identity" with murine PH-20 and human PH-20, "polyclonal antibodies against [guinea pig]PH-20 react only weakly with mouse sperm (unpublished results) or human sperm (38)."[159] This

---

[159] EX2013 (Lin 1993), 10075; *see also* EX2120 (Chan 1999), 1990 ("For example, the anti-gpPH-20 monoclonal antibodies do not cross-react with PH-20 from other species (13). The polyclonal sera directed against one type of PH-20 react only weakly with other types (13).").

lead researchers in 1993 to conclude that "[t]o test contraceptive efficacy in a certain species, ***PH-20 from that species must be used as immunogen***, such as monkey PH-20 to test in monkey and mPH-20 to test in mouse, etc."[160] This would have informed a POSA's expectation and would have led them to conclude that a modified PH20 polypeptide, which is a modified human polypeptide, would not be useful in eliciting a quality polyclonal response against relevant native PH20 epitopes in nonhuman mammals for purposes of immunocontraception.

B. A POSA would not have expected modified PH20 polypeptides to be useful as immunocontraceptive vaccines based on theoretical binding in humans and other mammals.

103. Dr. Cherr stated in his declaration that by December 28, 2012, "POSAs would have expected the polyclonal antibodies generated in female mammals (including humans) in response to ***any*** of the modified PH20 polypeptides… (appropriately administered as vaccines) would cause contraception by binding to sperm PH20 polypeptide in the female reproductive tract."[161] This opinion is based, in part, on his view that "POSAs would have known that the binding of antibodies to sperm PH20 polypeptide in the female

---

[160] EX2013 (Lin 1993), 10075.

[161] EX2072 (Cherr Dec.), ¶ 43 (emphasis added).

reproductive tract would cause contraception ***irrespective*** of where the antibodies bind on the PH20 polypeptide."[162] I disagree because more than mere binding is required for therapeutic efficacy.

104. A POSA would have understood that the possibility of eliciting antibody responses with contraceptive activity requires both binding *in vivo* and avid binding to the domain or domains of native PH20 necessary for fertilization.[163] As addressed above in Section VI.A.2, the polyclonal response to modified PH20 polypeptides would likely be heavily skewed towards the modified regions of the antigen which have no corresponding region in the native PH20. Denatured or misfolded modified PH20 polypeptides would be even less likely to yield antibodies to critical native epitopes, as discussed in Section VI.A.3.

105. A POSA would have expected that meaningful contraception (and certainly the near-100% contraceptive activity Dr. Cherr stated would be necessary for modified PH20 polypeptides to be useful antigens) could only be achieved with antibody responses that are specific to native epitopes implicated in reproductive

---

[162] EX2072 (Cherr Dec.), ¶ 33 (emphasis added).

[163] EX2010 (Primakoff 1988), 544; EX1019 (Hardy 2004), 330-332; Section V.B.

function and that are sufficiently strong to carry out immune function.[164] A POSA would have expected that only a subset of modified PH20 polypeptides (if any) could elicit such a meaningful immune response. Determining which of the many possible modified PH20 polypeptides could reliably elicit contraceptive antibody responses could only be determined empirically.[165]

106. Contrary to Dr. Cherr's suggestion that binding location does not matter, researchers in 1999 sought to understand the nature of the immune response in guinea pigs that caused contraception.[166] These researchers recognized that "[m]ammalian gamate [sic] fusion involves multiple steps and is in most cases species specific," that PH20 has more than one functionality, and that "multiple isoforms of the protein exist in the sperms of a given mammalian species."[167]

---

[164] EX1202 (Redwood 2007), 699 ("However, breaking self-tolerance may not be sufficient for immunocontraception, as autoimmune responses are not necessarily linked to altered physiology [22]. Consequently, for immunocontraception it is necessary to break tolerance, and for the response to be sufficient in quantity or quality to result in infertility."); EX2010 (Primakoff 1988), 544; EX1019 (Hardy 2004), 330-332; Section V.B.

[165] EX1202 (Redwood 2007), 699 ("Given these complexities it is not possible to determine, except empirically, which antigens will make a suitable target for immunocontraception.").

[166] EX2120 (Chan 1999).

[167] EX2120 (Chan 1999), 1998.

Though they sought to find linear epitopes on guinea pig PH20 (gpPH-20) the researchers reported results that "indicated the epitope sequence is conformation sensitive and likely to be discontinuous."[168] They also found two immunodominant and surface accessible regions that they hypothesized served different functions.[169] Importantly, they acknowledged that further research was required to dissect gpPH20 functions and that such experiments "are important to the ultimate definition of PH-20 ***structure*** as it relates to the development of a peptide-based contraceptive vaccine."[170]

107. Similarly, the Hardy 2004 authors suggested that their inability to impair fertility in mice was not due to insufficient titer but potentially the failure of the recombinant mPH20 antigen to replicate a critical epitope for reproduction found in the native PH20.[171] In fact, all of the animal experimental data available by the relevant timeframe would have reinforced a POSA's expectation that merely eliciting a polyclonal response that was reactive to native PH20 was insufficient to

---

[168] EX2120 (Chan 1999), 1993.

[169] EX2120 (Chan 1999), 1999.

[170] EX2120 (Chan 1999), 1999.

[171] EX1019 (Hardy 2004), 332.

achieve contraception.[172]

108. Dr. Cherr's rationale appears to be that as long as the antibodies bind to sperm, they would be expected to cause infertility.[173] He also invokes a number of theoretical mechanisms by which antibodies against sperm could contribute to contraception, "*e.g.*, inhibiting sperm motility, inducing sperm agglutination, reducing penetration of cervical mucus by sperm, interfering with sperm capacitation or the acrosome reaction, or stimulating sperm lysis via the complement pathway" and "allosteric effects."[174] Presumably, Dr. Cherr believes these effects would occur even if antibodies do not actually bind and inhibit a native PH20 epitope that is relevant to reproduction.

109. I disagree that a POSA would have expected such non-PH20-specific mechanisms to play a significant role in causing infertility. None of the papers Dr. Cherr cited for these mechanisms relate to PH20—they address anti-sperm antibody.[175] Anti-sperm antibodies are not necessarily specific to a particular sperm-protein (such as PH20) and may bind multiple and distinct targets on sperm,

---

[172] *See* Section V.B.

[173] *See* EX2072 (Cherr Dec.), ¶ 32.

[174] EX2072 (Cherr Dec.), ¶¶ 33–34.

[175] *See* EX2072 (Cherr Dec.), ¶ 33.

including in locations where PH20 is not expressed. Thus, the effects of anti-sperm antibodies are highly variable, context dependent, and often non-determinative, as confirmed in the literature Dr. Cherr cited. Dr. Cherr did not explain why a POSA would have expected anti-PH20 antibodies to cause contraception through the same mechanisms as these non-specific interactions and did not identify any experimental evidence justifying such extrapolation.

110. Other mechanisms identified by Dr. Cherr are even more general and less likely to be implicated as the main mechanism of contraception. Agglutination requires single antibody molecules to bridge two antigens (here, two spermatozoa). A POSA would recognize a number of factors would influence the likelihood of such an occurrence, including the quantity of antigen, the locations of expression of antibody-specific epitopes on such antigen (*i.e.* whether they are in positions for a single antibody to be capable of bridging both epitopes), the affinity and avidity of binding, and the isotypic composition of the antibody response, to name a few. A POSA could not have formed expectations of how anti-PH20 antibodies would behave from earlier reported studies of anti-sperm antibodies without knowing more regarding the nature of the anti-sperm antibodies.

111. Lysis via the complement pathway, or complement fixation, requires complement to be present in the mucosal fluids and sperm antibody isotypes capable of fixing complement. IgA does not fix complement via either the

traditional or alternative pathways.[176] The female reproductive tract is part of the secretory immune system "which utilizes secretory IgA as the predominant immunoglobulin in external secretions."[177] While IgA is produced locally in the reproductive tract, at least a portion is also serum-derived IgA. IgG and IgM may also be present, with reports suggesting IgG present in oviductal fluids are serum-derived.[178] A POSA would not have expected complement fixation to play a significant role in PH20-derived immunocontraception. If that POSA followed Dr. Cherr's directive to administer the modified PH20 polypeptide immunogen by a mucosal route, then they would expect a preferential, polyclonal IgA response, particularly in the oviduct at the site of fertilization. And if a POSA sought to induce complement fixation, then they would more likely have preferred systemic routes of administration to produce serum IgG, which was known to be present in the relevant reproductive sites through transudation from serum.[179]

112. Finally, it is unclear what precisely Dr. Cherr meant by "allosteric

---

[176] EX1203 (Russel 1989), 175; EX1204 (Nikolova 1994), 275.

[177] EX2114 (Frayne 1999), 13.

[178] EX2114 (Frayne 1999), 17.

[179] EX2114 (Frayne 1999), 17; EX1120 (Huo 2012), 3–4, Figure 3, Figure 4.

effects."[180] Allosteric inhibition of functional sites relevant to reproduction carries with it the same problems addressed earlier in regard to identifying and preserving relevant functional sites—or stretches close to them—in the modified PH20 antigen. Allosteric changes (*i.e.* distortion of the native PH20 structure) caused by bound antibody could possibly reduce or block hyaluronidase activity, but by the same logic, they could enhance it. Regardless, any allosteric change in PH20 functional sites by antibody binding to some distal site would depend on a number of unlikely events. An antibody capable of doing so would have to have an exceptionally high affinity such that binding with just one "arm" has sufficient strength to distort not only the epitope it binds but also the distal functional site.[181] Allosteric changes are typically only observed in highly unusual circumstances, and a POSA would not have expected them to play a role without experimental evidence indicating the mechanism is relevant for immunocontraception.

113. Overall, a POSA would have been concerned that antibody responses that did not block or neutralize a PH20 function necessary for fertilization, but instead reduced fertilization capacity by allostery or complement-fixation, might

---

[180] EX2072 (Cherr Dec.), ¶ 34.

[181] EX1205 (Goodey 2008), Abstract.

not cause meaningful contraception, let alone meet the near-100% efficacy level noted by Dr. Cherr.[182] In the context of viruses, both neutralizing antibodies that block virus entry into cells, thereby preventing infection, and antibodies that limit virus proliferation in the infected host, reducing morbidity, are often elicited. But while isotype-dependent antibody effector functions may enhance protection against infection by lower avidity neutralizing antibodies, the capacity for neutralization remains paramount. Similarly for contraception, blocking, not reducing, fertilization is the goal. Thus, a POSA would have expected the blocking of native PH20 epitopes implicated in fertilization to be the necessary objective, even if non-specific antibody responses could enhance protection.

114. In sum, a POSA would have expected that more than simply polyclonal antibody binding to native PH20 would be required to achieve infertility. A POSA could not have predicted which of the many possible modified PH20 polypeptides could elicit the right antibody response to cause contraception without empirical testing. In view of the experimental evidence using species-appropriate native PH20 antigens in animal models that was available by the relevant timeframe, a POSA would not have expected any modified (91% identity)

---

[182] *See* ¶¶ 52, 57, 104, 105 above.

PH20 polypeptide to be useful as contraceptive vaccines in humans or nonhuman mammals.

C. A POSA would not have expected adjuvants, boosters, and other helpful molecules to overcome the problems of a poor immunogen.

115. Both Drs. Moon and Cherr opined on mechanisms to magnify an immune response available to a POSA by the relevant timeframe. Dr. Moon referred to techniques including mucosal administration, adjuvants, booster doses, and overcoming tolerance.[183] Dr. Cherr likewise referred to mucosal administration, adjuvants, booster doses, and the addition of agents to remove β-defensin DEFB126 and unmask PH20 on sperm.[184] None of the techniques that Drs. Moon and Cherr identified to magnify the immune response are relevant to or overcome the problems I have identified above in Section VI.A–B.

116. While adjuvants and booster doses magnify immune responses, they

---

[183] EX2074 (Moon Dec.), ¶¶ 24–32, 46, 58.

[184] EX2072 (Cherr Dec.), ¶¶ 38, 55. Dr. Cherr stated that in his opinion, in order for modified PH20 polypeptides to be useful as contraception, they would have to be delivered mucosally. I note this requirement of mucosal administration is inconsistent with the Primakoff guinea pig experiments (which used subcutaneous injection to immunize experimental subjects) and it is not identified in the common disclosure as a necessary element to using modified PH20 polypeptides in contraceptive vaccines.

cannot alter the nature and quality of the antibody immune response. Thus, the problems of eliciting the right polyclonal antibodies (in spite of self-tolerance) that bind to the right locations on native PH20 to impair fertility using modified PH20 polypeptides that may be misfolded persist even with adjuvants and boosters.

117. Mucosal routes of administration could yield more antibody at the relevant reproductive sites. However, a POSA would have appreciated that subcutaneous immunization worked in guinea pigs and that systemic routes of administration are equally capable of eliciting strong antibody responses in relevant mucus tissue, as discussed above in Sections IV.E and V.B. Further, the route by which an antigen is introduced might change the epitopic specificities of antibodies generated in response because different T and B cells are distributed in the mucosal lymphoid tissues. But a POSA would not have assumed that mucosal administration would generally be better than systemic administration at generating the epitopic specificities required for contraception. And both routes must still go through central tolerance, as described in Sections IV.B. and VI.A.2. Making sperm-surface PH20 more accessible with an agent that removes β-defensin DEFB126, as Dr. Cherr suggests, also does not change the nature and quality of the antibody immune response.

118. Finally, it is unclear how Dr. Moon proposes using techniques such as "replacing some amino acids of the polypeptide self-antigen…with helper T Cell

epitope peptide, *e.g.*, PADRE (pan DR-binding epitope) peptide" would overcome tolerance in a way that ensures greater production of antibodies against self-epitopes.[185] Insertion of a PADRE sequence (which is 13 residues long) would still require an understanding of native PH20 structure and function to make sure the insertion does not disrupt any native conformations critical to reproduction. And even if a PADRE peptide could be inserted into a modified PH20 polypeptide in a way to preserve native conformation and overcome T-cell tolerance, B-cell tolerance would not be addressed. The low frequency of BCR reactive to self-epitopes resulting from B-cell tolerance would still be an issue, reducing the likelihood of a polyclonal response against native epitopes. Moreover, I am not aware of any approved vaccines that utilize the PADRE peptide.

VII. A POSA Would Have Needed to Make and Test Numerous Anti-PH20 Monoclonal Antibodies in Order to Find Ones That Could Be Useful for Contraception.

119. Both Drs. Cherr and Moon opined regarding delivering monoclonal antibodies against PH20 into the female vaginal cavity to cause contraception.[186] It is not clear how this relates to using modified PH20 polypeptides as antigens in

---

[185] EX2074 (Moon Dec.), ¶ 32.

[186] EX2074 (Moon Dec.), ¶¶ 60–63; EX2072 (Cherr Dec.), ¶¶ 57–61.

contraceptive vaccines.

120. Monoclonal antibodies are not the "modified PH20 polypeptides" that are the subject of the '618 Patent. To the extent they are used to cause contraception, monoclonal antibodies against PH20 would not be administered as a vaccine antigen. I understand Dr. Cherr confirmed he shares this same understanding.[187]

> 4 Q. These monoclonal antibodies are not being
> 5 administered as immunocontraceptive vaccines,
> 6 right?
> 7 A. Correct, they are being added to the
> 8 vaginal cavity.
> 9 Q. And modified PH20 polypeptides are not
> 10 monoclonal antibodies, right?
> 11 A. Yes, you're right on that.

(EX1129 (Cherr Dep.), 158:4–11.)

121. Dr. Cherr suggested in his declaration that anti-PH20 monoclonal antibodies to cause contraception could be "generated in response to any of the modified PH20 polypeptides…."[188] Dr. Cherr did not identify any evidence that modified PH20 polypeptides had been used to generate such antibodies.

---

[187] EX1129 (Cherr Dep.), 158:4–11.

[188] EX2072 (Cherr Dec.), ¶ 61.

122. Assuming that modified PH20 polypeptides can include polypeptides that may or may not be properly folded, it is difficult to imagine why a POSA would use any of the many possible modified PH20 polypeptides to generate and identify suitably contraceptive anti-PH20 monoclonal antibodies. Identifying anti-PH20 monoclonal antibodies that can impair fertility would require empirical testing, not only of modified PH20 polypeptides (which may or may not be properly folded) to identify a suitable antigen, but also of many antibodies to identify a suitable clone that binds with specificity and avidity to native PH20 epitopes that are relevant to reproductive function in a given species. Specificity for reproductively relevant epitopes and binding strength are even more significant issues with monoclonal antibodies that, by definition, are specific for only one epitope. And because PH20 has more than one function relevant to fertilization, it is likely that monoclonal antibodies to multiple different targets would need to be identified and tested in combination to achieve infertility.[189] Using modified PH20 polypeptides to generate anti-PH20 monoclonal antibodies (as Dr. Cherr

---

[189] Dr. Cherr appears to acknowledge this fact as well, as he states "POSAs would have selected well-known, routine systems to deliver a combination of different monoclonal antibodies that bind to PH20 polypeptide of sperm, each binding to different epitopes on the sperm PH20 polypeptide, similar to the polyclonal antibodies generated in response to modified PH20 polypeptide vaccines." EX2072 (Cherr Dec.), ¶ 59.

apparently suggests) would therefore be the start of a very long research project to identify suitable antigens and antibodies.

VIII. Conclusion

123. As I explained in Section V, by the relevant timeframe in December 2011, a POSA would not have found the universal use of modified PH20 polypeptides as antigens in contraceptive vaccines to be credible in males or females based upon available experimental evidence using native PH20.

124. As I explained in Section VI, a POSA could not have expected that any and all of the many possible modified PH20 polypeptides would 1) elicit polyclonal antibody responses against native PH20 in female humans and nonhuman mammals and 2) cause infertility in female humans and nonhuman mammals when administered as a vaccine. A POSA could not have known which of the many possible modified PH20 polypeptides could escape tolerance and yield a quality antibody response sufficient to block the native PH20 fertilization functions without empirical testing.

125. As I explained in Section VII, monoclonal antibodies are not modified PH20 polypeptides. If a POSA even thought to use modified PH20 polypeptides as starting antigens, that POSA would have to engage in substantial empirical testing to identify suitable modified PH20 polypeptide starting antigens and monoclonal antibodies for contraception.

I, Garnett Kelsoe, do hereby declare and state, that all statements made herein of my own knowledge are true and that all statements 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, under Section 1001 of Title 18 of the United States Code.

Executed on: May 8, 2026

Appendix A - Exhibit List

No.	Exhibit Description
EX1001	U.S. Patent No. 12,037,618
EX1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
EX1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
EX1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
EX1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
EX1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
EX1026	U.S. Patent Application No. 13/694,731
EX1045	Redline Comparison of the '731 App. and 12,037,618 Patent
EX1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J., 17:1144-1156 (2015)
EX1119	Csoka, A. et al., "The Six Hyaluronidase-Like Genes in the Human and Mouse Genomes" Matrix Biology 20:499-508 (2001)
EX1120	Huo, Z. et al., "Systemic and Mucosal Immune Responses to Sublingual or Intramuscular Human Papilloma Virus Antigens in Healthy Female Volunteers," PLoS ONE 7(3):e33736 (2012)
EX1122	Printz, M. et al., "Risk Factors, Hyaluronidase Expression, and Clinical Immunogenicity of Recombinant Human Hyaluronidase PH20, an Enzyme Enabling Subcutaneous Drug Administration," AAPS 24(6):110 (2022)

No.	Exhibit Description
EX1129	Transcript of the Deposition of Dr. Gary Cherr, Ph.D., November 12, 2025
EX1132	Transcript of the Deposition of Dr. James Moon, Ph.D., November 18, 2025
EX1150	Chowpongpang, S. et al., "Cloning and Characterization of the Bovine Testicular PH-20 Hyaluronidase Core Domain," Biotechnol Lett., 26(15):1247-52 (2004)
EX1161	Primakoff, P. et al., "Purification of the guinea pig sperm PH-20 antigen and detection of a site-specific endoproteolytic activity in sperm preparations that cleaves PH-20 into two disulfide-linked fragments," Biology of Reproduction 38:921-934 (1988)
EX1162	Koch, C. et al., "A Comparison of the Immunogenicity of the Native and Denatured Forms of a Protein," APMIS 104:115-125 (1996)
EX1163	Leder, L. et al., "Genuine and Apparent Cross-Reaction of Polyclonal Antibodies to Proteins and Peptides," Eur. J. Biochem. 219:73-81 (1994)
EX1170	Murphy, K., "Janeway's Immuno Biology," (8th 2012), Chapters 1, 4, 8, 10, 11, 12, 15, and Appx I
EX1171	Yang, X. et al., "An Introduction to Epitope Prediction Methods and Software," Rev. Med. Virol., 19: 77–96 (2009)
EX1172	Bolland, S., "An Innate Path to Human B Cell Tolerance," Immunity, 29(5):667-9 (2008)
EX1173	Anderson, M. et al., "Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein," Science, 298(5597):1395-401 (2002)
EX1174	Yewdell, J. et al., "Immunodominance in Major Histocompatibility Complex Class I-restricted T Lymphocyte Responses," Annu. Rev. Immunol., 17:51–88 (1999)
EX1175	Popova, L. et al., "Immunodominance of Antigenic Site B over Site A of Hemagglutinin of Recent H3N2 Influenza Viruses," PLoS One, 7(7):e41895 (2012)

No.	Exhibit Description
EX1176	Gershoni, J. et al., "Epitope Mapping: The First Step in Developing Epitope-Based Vaccines," BioDrugs, 21(3):145-56 (2007)
EX1177	Rolland, M. et al., "Recognition of HIV-1 Peptides by Host CTL Is Related to HIV-1 Similarity to Human Proteins," PLoS One, 2(9):e823 (2007)
EX1178	Nelson, C. et al., "Peptides Determine the Lifespan of MHC Class II Molecules in the Antigen-Presenting Cell," Nature, 371(6494):250-2 (1994)
EX1179	Dormitzer, P. et al., "Influenza Vaccine Immunology," Immunol Rev., 239(1):167-77 (2011)
EX1180	Mantis, NJ., et al., "Secretory IgA ' s Complex Roles in Immunity and Mucosal Homeostasis in the Gut," Mucosal Immunol., 4(6):603-11 (2011)
EX1181	Siskind, G. and Eisen, H., "Effect of Variation in Antibody-Hapten Association Constant upon the Biologic Activity of the Antibody," J Immunol., 95(3):436-41 (1965)
EX1182	Levine, B. and Levytska, V., "A Sensitive Hemagglutination Assay Method for Dinitrophenyl-Specific Antibodies. The Effect of Antibody Binding Affinity on Titers," J Immunol., 98(3):648-52 (1967)
EX1183	Fauci, A. et al., "The Relationship between Antibody Affinity and the Efficiency of Complement Fixation," J Immunol., 105(1):215-20 (1970)
EX1184	Laver, W. et al., "Epitopes on Protein Antigens: Misconceptions and Realities," Cell 61:553-556 (1990)
EX1185	Lu, X. et al., "Anti-gp160 IgG and IgA Antibodies Associated with a Large Increase in Total IgG in Cervicovaginal Secretions from Human Immunodeficiency Virus Type l-Infected Women," Journal of Infectious Disease, 167(5):1189-92 (1993)
EX1186	Kemp, T. et al., "Evaluation of Systemic and Mucosal Anti-HPV16 and Anti-HPV18 Antibody Responses from Vaccinated Women," Vaccine, 26(29-30):3608-16 (2008)
EX1187	Montefiori, D. et al., "Magnitude and Breadth of the Neutralizing Antibody Response in the RV144 and Vax003 HIV-1 Vaccine

No.	Exhibit Description
	Efficacy Trials," Journal of Infectious Disease, 206(3):431-41 (2012)
EX1188	Cherr, G. et al., "The Dual Functions of GPI-Anchored PH-20: Hyaluronidase and Intracellular Signaling," Matrix Biol., 20(8):515-25 (2001)
EX1189	Martin-Deleon, P., "Epididymal SPAM1 and its Impact on Sperm Function," Molecular and Cellular Endocrinology 250:114-121 (2006)
EX1190	Nolan, R. et al., "The Safety of Recombinant Human Hyaluronidase PH20 in Nonclinical Models: An Overview of Toxicology, Pharmacology, and Impact of Anti-PH20 Antibodies," Journal of Controlled Release, 374:369-383 (2024)
EX1191	McCutcheon, J. et al., "HLA-B*0702 Antibody Epitopes are Affected Indirectly by Distant Antigen Residues," Hum Immunol., 36(2):69-75 (1993)
EX1192	Nobusawa, E. et al., "Comparison of Complete Amino Acid Sequences and Receptor-Binding Properties among 13 Serotypes of Hemagglutinins of Influenza A Viruses," Virology, 182(2):475-85 (1991)
EX1193	CDC Press Release: "Highly Pathogenic Avian Influenza A (H5N1) Virus Infection Reported in a Person in the U.S." (Apr. 1, 2024)
EX1195	Zhang, H. et al., "Mouse Spam1 (PH-20) Is a Multifunctional Protein: Evidence for Its Expression in the Female Reproductive Tract," Biol Reprod., 69(2):446-54 (2003)
EX1196	Dunn, C. et al., "Transcription of the Human and Rodent SPAM1 / PH-20 Genes Initiates Within an Ancient Endogenous Retrovirus," BMC Genomics, 6:47 (2005)
Ex1197	Hirsch, C. et al., "The Ubiquitylation Machinery of the Endoplasmic Reticulum," Nature, 458(7237):453-60 (2009)
EX1198	Singh, S., et al., "Solubilization and Refolding of Bacterial Inclusion Body Proteins," Journal of Bioscience and Bioengineering 99:303-310 (2005)

No.	Exhibit Description
EX1199	Li, M. et al., "Importance of Glycosylation and Disulfide Bonds in Hyaluronidase Activity of Macaque Sperm Surface PH-20," J Androl., 23(2):211-9 (2002)
EX1201	Rodriguez, L. et al., "Foot and mouth disease virus vaccines," Vaccine 27:D90-D94 (2009)
EX1202	Redwood, A. et al., "Viral Vectored Immunocontraception: Screening of Multiple Fertility Antigens using Murine Cytomegalovirus as a Vaccine Vector," Vaccine, 25(4):698-708 (2007)
EX1203	Russell, M. et al., "Complement-Fixing Properties of Human IgA Antibodies. Alternative Pathway Complement Activation by Plastic-Bound, but not Specific Antigen-Bound, IgA," Scand J Immunol., 30(2):175-83 (1989)
EX1204	Nikolova E. et al., "All Forms of Human IgA Antibodies Bound to Antigen Interfere with Complement (C3) Fixation Induced by IgG or by Antigen Alone," Scand J Immunol., 39(3):275-80 (1994)
EX1205	Goodey, N. et al., "Allosteric Regulation and Catalysis Emerge via a Common Route," Nat Chem Biol. 4(8):474-82 (2008)
EX2010	Primakoff, P., et al., "Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20," Nature 335:543-546 (October 6, 1988)
EX2013	Lin, Y., et al., "Molecular cloning of the human and monkey sperm surface protein PH-20," Proc. Natl. Acad. Sci USA 90:10071-10075 (November 1993)
EX2072	Declaration of Gary N. Cherr, Ph.D. in Support of Patent Owner's Response
EX2074	Declaration of James J. Moon, Ph.D. in Support of Patent Owner's Response
EX2108	Hunnicutt, G. et al., "Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity is Required in Secondary Sperm-Zona Binding," Biology of Reproduction, 55:80-86 (1996)

No.	Exhibit Description
EX2114	Frayne, J. et al., "The potential use of sperm antigens as targets for immunocontraception; past, present and future," Journal of Reproductive Immunology, 43:1-33 (1999)
EX2119	Myles, D. et al., "Localized Surface Antigens of Guinea Pig Sperm Migrate to New Regions Prior to Fertilization," The Journal of Cell Biology, 99:1634-1641 (1984)
EX2120	Chan, C. et al., "Identification of Linear Surface Epitopes on the Guinea Pig Sperm Membrane Protein PH-20," Life Sciences, 64(22):1989-2000 (1999)
EX2137	Lipman, N. et al., "Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources," ILAR Journal, 46(3):258-268 (2005)
EX2167	Huang, C. et al., " Effect of sublingual administration with a native or denatured protein allergen and adjuvant CpG oligodeoxynucleotides or cholera toxin on systemic TH2 immune responses and mucosal immunity in mice," Annals of Allergy, Asthma, and Immunology, 99:443-452 (November 2007)

Appendix B – CV

CURRICULUM VITAE

November 2025

Garnett Herrel Kelsoe III

James B. Duke Professor of Immunology
Departments of Integrative Immunobiology and Surgery
Duke Human Vaccine Institute
School of Medicine, Duke University
27 Alexandria Way, Suite 100, RTP Campus
Durham, North Carolina 27713

Telephone:
Office: (919) 613-7815
Home: (919) 402-1462

Fax: (919) 613-7878

E-mail: ghkelsoe @ duke.edu

Citizenship: USA
Date of Birth: December 8, 1949
Social Security Number: *on request*

EDUCATION

1972 Southern Methodist University, Dallas, Texas. B.S.
Major: Biology

1974 Southern Methodist University, Dallas, Texas. M.S.
Major: Biology (Parasitology)

1975 Harvard University, Boston, Massachusetts. M.Sc.
Major: Tropical Public Health (Parasitology)

1979 Harvard University, Boston, Massachusetts. D.Sc. in Tropical Public Health and Microbiology. Special Field: Immunology
(T.H. Weller, advisor)

1979-1982 Research Fellow, Institute for Genetics, University of Cologne, Cologne, Federal Republic of Germany
(K. Rajewsky, advisor)

1. APPOINTMENTS

2020-present Associate Professor, Department of Surgery, Surgical Sciences.
Duke University School of Medicine

2012- Scientific Leadership Group, Center for HIV/AIDS Vaccine Immunology –

present	Immunogen Design and Center for HIV/AIDS Vaccine Design (CHAVI-ID and CHAVD)

(Appointments, *continued*)

2006-2012	Associate Director, Bill and Melinda Gates Foundation Duke Vaccine Antibody Consortium
2002-2005	External Faculty Member, The Santa Fe Institute
2001-present	James B. Duke Professor of Immunology, Duke University
1999-present	Senior Fellow, Duke Center for the Study of Aging and Human Development, Duke University School of Medicine; Member, Duke Comprehensive Cancer Center, Duke University School of Medicine.
1999-2006	Director of Graduate Studies in Immunology, Duke University School of Medicine
1998-Present	Professor, Department of Immunology, Duke University School of Medicine.
1994-1998	Professor, Department of Microbiology and Immunology, University of Maryland School of Medicine.
1989-1994	Associate Professor, Department of Microbiology and Immunology, University of Maryland School of Medicine.
1988-1989	Associate Professor, Department of Microbiology. University of Texas Medical Branch, Galveston, Texas.
1982-1988	Assistant Professor, Department of Microbiology, University of Texas Medical Branch, Galveston, Texas.
1979-1982	Research Fellow, Institute for Genetics, University of Cologne, Cologne, Federal Republic of Germany.

TEACHING

Harvard University: Medical Parasitology.

University of Texas Medical Branch: Introductory- (Medical School) and Advanced Immunology, Immunogenetics (Graduate School), and Immunology for nursing and physical therapist students.

University of Maryland School of Medicine: Director, Microbiology and Immunology Graduate Program, 1990-1994. Immunology (Medical School), Immunogenetics, Basic Immunology, and Immunology Core Course (Graduate School). Human Genetics (Graduate School).

Johns Hopkins University School of Medicine: Immunology (Architecture of immune responses; Medical and Graduate Schools), 1997.

(Teaching, *continued*)

Duke University School of Medicine: Introductory (*Imm244, Imm544*) and Advanced Immunology (*Imm291, Imm800*), Tumor Immunology (*Imm300*), Immunity and Pathogenesis (co-director; *Imm310*), Mathematical Immunology (Graduate School); Body and Disease (course director, immunology; Medical School).

National/International: Faculty, First International School on Cellular and Molecular Immunology (Kobuleti, Georgia, USSR), 1989. Faculty, Australian Society for Immunology – Federation of Immunological Societies of Asia-Oceania Advanced Immunology Course (Canberra, Australia), 1996. Faculty, Cold Spring Harbor Laboratory Course on Phage Antibodies (Cold Spring Harbor, USA), 1995-2000. Faculty, EMBO Practical Course on Lymphocyte Development (Basel, Switzerland), 1997. Faculty, German Society for Immunology Advanced Course in Immunology (Ettal, Germany), 2006. Faculty, Shanghai Institute for Immunology Summer School, Shanghai Jiao Tong University School of Medicine (Shanghai, China), 2018, 2019.

AWARDS and HONORS

National Institutes of Health Institutional Predoctoral Fellowship, Harvard University, 1975.

Rockefeller Foundation Fellowship, Harvard University, 1976-1979.

National Science Foundation National Needs Postdoctoral Fellowship, Institute for Genetics, University of Cologne, 1979-1980.

European Molecular Biology Organization Long Term Fellowship, Institute for Genetics, University of Cologne, 1981-1982.

Wellcome Visiting Professorship in the Basic Medical Sciences, University of Iowa College of Medicine, 1995.

Visiting Scientist, the Jeanne M. and Joseph P. Sullivan Program in Theoretical Immunology, Santa Fe Institute, 1997.

Nina W. Werblow Lectureship, Cornell University School of Medicine, 1998.

James B. Duke Endowed Professorship, Duke University, 2001.

External Faculty Appointment, The Santa Fe Institute, 2002-2008.

Norman L. Letvin Scholar Award, Duke CHAV-ID Consortium, 2018.

Pinnell Symposium Lecture, Duke University School of Medicine, 2019.

Duke CHAVD Scholar Award, NIH CHAVD Consortia, 2020 (shared with F.W. Alt).

Keynote Address, Keystone Symposium: B Cell – T Cell Collaboration, Hannover Germany, 2022

Buch Lecture (IX), Max Delbruck Center for Molecular Medicine, Berlin Germany, 2022.

Sigma Xi, 2025.

(Awards and Honors, *continued*)

*Pillar of Immunolog*y listing, 2025: Jacob *et al*. Intraclonal generation of antibody mutants in germinal centres. Nature (Lond.) *354*: 389-392; 1991. American Association of Immunologists; G.D. Victora nominator.

TRAINEES

Undergraduate	**Placement**
Sergei B. Koralov, B.S. Duke University (honors thesis) 1999-2000	Graduate Student Harvard University Boston, Massachusetts
Alexandra D. Floyd, B.S. Duke University (honors thesis) 1999-2000	Medical Student University of Maryland School of Medicine Baltimore, Maryland
Johannes Graumann, Diplom Biol. University of Konstanz, FRG (*Diplom* thesis) 1999-2000	Graduate Student California Institute of Technology Pasadena, California
Karyn Rose Singer, B.S. Duke University (honors thesis) 2000-2001	Graduate Student Cambridge University Cambridge, England
Ruth McMillan, M.S. North Carolina Central University 2002 – 2004	Graduate Student North Carolina St. University Raleigh, North Carolina
Emily Heikamp, B.S. Duke University 2002 – 2005	Graduate Student (Marshall Scholar) Oxford University Oxford, England
Anjali Patel, B.S. Duke University 2005	Research technician Duke University Durham, North Carolina
Kim Cocce, B.S. Duke University 2007-2008	M.D. /Ph.D. Student School of Medicine Duke University Durham, North Carolina

Graduate/Medical	**Placement**
Douglas K. Schreiber, M.D. University of Texas Medical Branch Galveston (honors thesis) 1988	Residency Training University of Texas Medical Branch Galveston, Texas
Joshy Jacob, Ph.D. University of Maryland School of Medicine, 1988-1992	Postdoctoral Fellow Massachusetts Institute of Technology Cambridge, Massachusetts Dr. D. Baltimore, advisor
(Graduate/Medical Trainees, *continued*)	
Carla Miller, Ph.D. University of Maryland School of Medicine, 1990-1995	Postdoctoral Fellow NIAID, NIH Bethesda, Maryland Dr. R. Schwartz, advisor
Xu Liu, M.S. University of Maryland School of Medicine, 1993-1995	Research Technician Merck & Co., Inc. West Point, Pennsylvania
Joseph Dal Porto, Ph.D. University of Maryland School of Medicine, 1992-1997	Postdoctoral Fellow National Jewish Center for Medical Research, Denver, Colorado Dr. J. Cambier, advisor
Michiko Shimoda, Ph.D. University of Maryland School of Medicine, 1995-1997	Research Fellow University of Tokyo Department of Applied Microbiology Tokyo, Japan Dr. S. Kaminogawa, advisor
Zhibin Chen, M.D., Ph.D. Duke University School of Medicine, 1995-2000	Postdoctoral Fellow Harvard University Boston, Massachusetts Dr. D. Mathis, advisor
Kaiyong Yang, Ph.D. Duke University School of Medicine, 1997-2003	Postdoctoral Fellow Harvard University Boston, Massachusetts Dr. H. Weiner, advisor
Marco L. Davila, M.D., Ph.D. Duke University School of Medicine (MSTP candidate) 1998-2004	Residency Training (Internal Medicine) Cornell University Hospitals New York, New York

Fiefei Liu, M.D., Ph.D. Duke University School of Medicine 2004-2007	Postdoctoral Fellow Harvard University Boston, Massachusetts Dr. K. Georgopoulos, advisor
Derek Cain, Ph.D. Duke University School of Medicine 2005-2010	Postdoctoral fellow Duke University Dr. G. Kelsoe, advisor
T. Matthew Holl, Ph.D. Duke University School of Medicine 2005–2010	Scientific Consultant Becton-Coulter Research Triangle Park, North Carolina

(Graduate/Medical Trainees, *continued*)

Pilar Snowden, Ph.D. Duke University School of Medicine 2006-2012	Federal Drug Administration Scientific Process Administration Washington, DC
Kathleen O'Hara, M.A. Duke University School of Medicine 2007-2009	Veterinary Medicine Student College of Veterinary Medicine Cornell University
Alexander Reynolds, Ph.D. Duke University School of Medicine 2010-2016	Consultant Quintiles Transnational, Inc. New York, New York
Guang Yang, Ph.D. Duke University School of Medicine 2010-2015	Consultant McKinsey and Co. Charlotte, North Carolina
Kuei-Ying Su, M.D., Ph.D. Duke University School of Medicine 2011-2015	Staff Rheumatologist Hualien Tzu Chi General Hospital Hualien City, Taiwan
Joel Finney Duke University School of Medicine 2015-2021	Postdoctoral Fellow Department of Immunology Dr. G. Kelsoe, advisor

Postdoctoral	**Placement**
Vladimir V. Yurovsky, Ph.D. University of Maryland School of Medicine, 1990-1991	Assistant Professor (Non-tenure Track) University of Maryland School of Medicine Department of Medicine Baltimore, Maryland
Biao Zheng, M.D. Ph.D. University of Maryland School of Medicine, 1992-1996	Assistant Professor (Tenure Track) Baylor University School of Medicine

	Department of Microbiology and Immunology Houston, Texas
Shuhua Han, M.D. Duke University School of Medicine, 1993-1999	Assistant Professor (Tenure Track) Baylor University School of Medicine Department of Microbiology and Immunology Houston, Texas
Douglas M. Cerasoli, Ph.D. University of Maryland School of Medicine, 1996-1998	Principal Investigator (Tenure Track) U.S. Army Medical Research Institute Aberdeen, Maryland

(Postdoctoral Trainees, *continued*)

Yoshimasa Takahashi, Ph.D. University of Maryland School of Medicine, 1996-1998	Research Scientist (Tenure Track) National Institute of Infectious Disease Tokyo, Japan
Sandra J. Foster, Ph.D. Duke University School of Medicine 1998-2001	Senior Principal Scientist Artecel Sciences, Inc. Research Triangle Park, North Carolina
Limin Zhang, Ph.D. Duke University School of Medicine 2000-2001	Staff Scientist Cellular Technologies, Inc. Cleveland, Ohio
Lindsay Cowell, Ph.D. Duke University School of Medicine 2000-2003	Assistant Professor (Tenure Track) Duke University Department of Biostatistics and Bioinformatics Durham, North Carolina
Yoshihiro Ueda, Ph.D. Duke University School of Medicine 2001-2007	Lecturer (Tenured) Department of Molecular Genetics Kansai Medical University Osaka, Japan
Huiayong Chen, Ph.D. Duke University School of Medicine 2004-2008	Postdoctoral Fellow Department of Surgery Duke University Durham, North Carolina
Masayuki Kuraoka, Ph.D. Duke University School of Medicine 2006-2014	Assistant Professor (Non-Tenure Track) Department of Immunology Duke University Durham, North Carolina

Yang Liu, Ph.D. Duke University School of Medicine 2009-2010	Postdoctoral Fellow Department of Cell Biology University of North Carolina Chapel Hill, North Carolina
Laurie McWilliams, M.D. Duke University School of Medicine 2010-2011	Fellow in Pediatrics Department of Pediatrics Duke University Medical Center Durham, North Carolina
Derek Cain, Ph.D. Duke University School of Medicine 2010-2013	IRTA Fellow Laboratory of Signal Transduction NIEHS Research Triangle Park, North Carolina

(Postdoctoral Trainees, *continued*)

Takuya Nojima, Ph.D. Duke University School of Medicine 2011-2014	Leader, Immunology Research Unit Astellas Pharma, Inc. Tsukuba, Japan
Akiko Watanabe, Ph.D. Duke University School of Medicine 2014-2018	Research Scientist (Non-Tenure Track) Department of Immunology Duke University Durham, North Carolina
Chen-Hao Yeh, Ph.D. Duke University School of Medicine 2015-2022	Assistant Professor (Tenure Track) Department of Medicine Duke University Durham, North Carolina
Shengli Song, Ph.D. Duke University School of Medicine 2017-2022	Instructor Department of Surgery Duke University Durham, North Carolina
Ryutaro Kotaki, Ph.D. Duke University School of Medicine 2019-2021	Research Scientist (Tenure Track) Laboratory of Immunology National Institute of Infectious Disease Tokyo, Japan
Joel Finney, Ph.D. Duke University School of Medicine 2021-2023	Postdoctoral Fellow Department of Biochemistry & Molecular Biology Harvard University Boston, Massachusetts Dr. Stephen C. Harrison, advisor

Keisuke Tonouchi, Ph.D. Duke University School of Medicine 2023-present	Postdoctoral Fellow
John S. Barber, M.D. Duke University School of Medicine 2023-present	Postdoctoral Fellow

MEMBERSHIP IN PROFESSIONAL SOCIETIES

American Association of Immunologists
American Association for the Advancement of Science
New York Academy of Sciences
Sigma Xi
Texas Academy of Sciences (Patron)
Royal Society of Medicine (Overseas Associate)
International Society for Vaccines
Texas Navy Association (Commander)

ADDITIONAL INFORMATION

The Journal of Clinical Investigation: Deputy Editor (2012-2017)

The Journal of Immunology: Associate Editor (1989-1991); Section Editor (1991-1995); Deputy Editor (1997-2002)

BMC Immunology: Editorial Board (2004-present)

Faculty of 1000, Biology Reports Ltd.: Immunology/Leukocyte development (2001-2002).

Organizer (with P. Nelson) Duke University Conference on Mathematical Immunology (2000)

Director: University of Maryland Immunology Group (1994-1995)
Graduate Studies, Program in Immunology, Duke University (1999-2006)

Member: Biological and Clinical Aging Review Committee, N.I.H. (Subcommittee A 1990-1994; Chairman, 1993-1994)
Advisory Panel: Biology of Aging Program, National Institute on Aging (1991, 1994, 1998)
Immunological Sciences Study Section: *ad hoc* member, N.I.H. (1990, 1992, 1996)
External Reviewer: The Wellcome Trust, Imperial Cancer (1996, 1998, 2001-2003)
N.I.H. Reviewers Reserve (1994-present)
Research and Graduate Education Advisory Committee, University of Maryland School of Medicine (1995-1998)
Bressler Research Awards Committee (Chairman), University of Maryland School of Medicine (1995-1998)
Recombinant DNA Safety Committee (Chairman), University of Maryland at Baltimore (1996-1998)
Research Fund and International Human Frontier Science Program (1996-present)
Scientific Advisory Board, Institute for Advanced Studies on Immunology and Aging, Washington, D.C. (1996-present)
Council, Midwinter Conference of Immunologists, Big Bear Lake, California (1997-2000)

External Reviewer: Immunology Graduate Group, University of Pennsylvania (with H.O. McDevitt and M. Bevan; 1998)

(Additional information, continued)

Microbial Pathogenesis Task Force, Duke University Medical Center (1999)

Basic Science Faculty Steering Committee
Duke University Medical Center (1999-2003; 2005-2007; chair, 2006-2007)
Appointments, Promotions, and Tenure Committee, Basic Sciences
Duke University Medical Center (2001-2013; chair, 2012-2013)
National Institute of General Medical Sciences Advisory Committee
of the Santa Fe Institute (2001-2008)
Duke University Academic Council (2002-2018)
Hearing Committee (2004–2009)
Harassment Grievance Board (2010-2013)
Executive Board, Dedman College, Southern Methodist University (2003-2012)
External Reviewer: Graduate Program in Immunology, University of Toronto (with K. Knight: 2004)
Executive Committee of the Graduate Faculty, Duke University (2005-2007)
Chancellor's Science Advisory Council, Duke University Medical Center (2006-2010)
Duke University Medical Center Academic Affairs Committee, Duke University Medical Center (2010-2012)

Ad Hoc Editorial Reviews:

American Journal of Pathology
Arthritis & Rheumatism
Blood
eLIFE
EMBO Journal
European Journal of Immunology
Experimental Cell Research
Gene
Immunity
Immunogenetics
Immunology Today
International Immunology
Journal of Anatomy
Journal of Clinical Investigation
Journal of Experimental Medicine
Journal of Gerontology
Journal of Immunogenetics
Journal of Immunological Methods
Journal of Immunology
Journal of Leukocyte Biology
Journal of Theoretical Biology
Nature
Nature Communications
Nature Immunology
Nature Medicine

Nature Reviews Immunology
Oncogene
PLoS Biology
Proceedings of the National Academy of Sciences, U.S.A.

(Ad Hoc Editorial Reviews, continued)

Reviews in Mutation Research
Science
Science Immunology
Therapeutic Immunology
Trends in Immunology

Patents:

U.S. Patent No. 9,963,501 "*B cell lineage-based immunogen design with humanized animals*"

U.S. Patent No. 10,835,599 "*Methods to identify prime and boost antigens for use in a B cell lineage-based vaccination protocol*"

U.S. Patent No. 10,092,638 "*GP120 immunogens and methods inducing neutralizing antibodies to human immunodeficiency virus*"

U.S. Patent No. 89,269,95B2 "*Adjuvant*"

World Patent No. 2020/191181 A1 "*Monoclonal antibodies for the prevention and treatment of Herpes simplex viral infections*"

U.S. Patent No. 12, 459, 987 "*Monoclonal antibodies for the prevention and treatment of Herpes simplex viral infections"*

Consulting:

Fish & Neave, 1251 Avenue of the Americas, New York, New York

Dewey Ballantine, LLP, 1301 Avenue of the Americas, New York, New York

Richard J. Prendergast, Ltd., 111 West Washington Street, Chicago, Illinois

Ropes & Gray, 1251 Avenue of the Americas, New York, New York

Bristows, 3 Lincoln's Inn Fields, London WC2A 3AA

Powell Gilbert, LLP, 25 Southampton Buildings, Chancery Lane, London WC2A 1Al

Morrison & Foerster, LLP, 1290 Avenue of the Americas, New York, New York

Quinn Emanuel Urquhart & Sullivan, LLP, 51 Madison Avenue, New York, New York

RESEARCH INTERESTS

Large-scale clonal analyses of lymphocyte antigen-receptor repertoires, including the determination of paratopic frequencies and of the V(D)J gene rearrangements encoding particular antibody and T cell antigen-receptor phenotypes. Population structure of immune responses: *ex vivo* and *in situ* phenotypic and genotypic analyses. The germinal center reaction including *Ig* somatic hypermutation, class-switch recombination, immunological memory, lymphocyte activation and affinity-dependent selection. Recruitment and persistence of germinal center B cells with very low affinities for native antigen. Identification of T cells resident in germinal centers and the identification of their distinctive physiology. The effects of locality on the recruitment of memory B cells into secondary germinal center reactions. V(D)J rearrangement by peripheral B- and T-lymphocytes. Developmentally regulated expression of AID in immature and transitional B lymphocytes and the effects pf this process on B-cell tolerance. Regulation of hematopoiesis by innate immune responses and especially pro-inflammatory cytokines. Competition between hematopoietic lineages and identification of leukopoietic niches in bone marrow. The role of complement and complement receptors in regulating immune responses. Effects of immunological tolerance/regulation on immune responses to HIV-1 and the design of immunization strategies to mitigate these effects. The generation and selection of BCR repertoires to viral vaccines and pathogens.

RESEARCH AND TRAINING FUNDS

Active Support

NIH/NIAID UM1 AI 144371, Center for HIV/AIDS Vaccine Development (B.F. Haynes, PI) (project period: 07/15/2019 - 06/30/2026). TDC (subcontract only; G. Kelsoe) $1,750,000; 7 years. Goal: To generate novel vaccine immunogens that elicit protective, broadly reactive neutralizing serum antibody responses against HIV-1. These novel vaccines will be tested by identifying and recovering germinal center and memory B cells from peripheral lymphoid tissue and blood that are elicited by vaccine immunogens.
Role: project PI.

NIH/NIAID P01 AI 131251, SHIV Env antibody coevolution as a molecular guide to HIV-1 V3 glycan targeted vaccine design (G.M. Shaw, PI) (project period: 06/01/2022 – 05/31/2027). TDC (subcontract only; G. Kelsoe) $2,750,000; 5 years. Project Goal: To optimize humoral protection, determine the role of BCR affinity in the fates of B cells exposed to serial immunizations or chronic SHIV infection. Parallel studies in BCR knock-in mice and rhesus macaques will merge lineage tracing of GC B and T cells with high throughput transcriptional analysis of individual lymphocytes to determine the immunological environments that maximize production of broadly neutralizing antibody responses.
Role: project PI.

NIH/NIAID U19 AI 121471: The Risks and Opportunities of Homeostatic Repopulation (S. Kenechtle, PI); (project period 09/01/2022-08/31/2027) TDC (G. Kelsoe only) $500,000; 5 years. Goal: to determine the specificity and population dynamics of graft specific B cells following liver and kidney transplantations in macaques and humans.
Role: key personnel.

NIH/NIAID P01 AI 089618: Structure-function analysis of infection- and vaccine-induced B-cell repertoires (S.C. Harrison, PI); (project period: 12/01/2023 - 11/30/2028) TDC (G. Kelsoe only) $1,202,050; 5 years. Goal: to understand and characterize the nature of vaccine elicited, humoral memory.
Role: project PI.

NIH/NIAID R01 AI 175411, Overcoming humoral rejection after xenotransplantation in sensitized non-human recipients (J Kwun, PI); (project period: 02/06/2023 – 01/31/2028) TDC (G.Kelsoe only) $100,000; 5 years. Goal: to evaluate methods for desensitization and immunosuppression to promote long-term xenograft survival.
Role: Co-Investigator.

NIH/NIAID Contract BAA-75N93023R00002, Innovations in Functional B Cell Epitope Discovery (G. Kelsoe and M. Kuraoka, co-PIs); (project period: 09/30/2024 - 09/29/2029) TDC $5,020,059; 5 years. Goal: to identify and structurally characterize all influenza HA and NA epitopes recognized by a diverse population of infected/vaccinated humans.
Role: PI.

Pending Support

None.

Past Support

NIH/NIAID R01 AI128832 Immunity to novel T/F SHIVs: variability in the co-evolution of virus and host immunity (G. Kelsoe, PI); (project period 07/01/2017-30/06/2022). Role: PI.

NIH/NIAID P01 AI131251 SHIV/HIV Env-Antibody Coevolution as a Guide to Iterative Vaccine Design (G. Shaw, PI); (project period 4/1/2017 – 3/31/22). Role: project PI.
(Research and training funds, *continued*)

NIH/NIAID P01 AI089618 Structure-function analysis of infection- and vaccine-induced B-cell repertoires (S.C. Harrison, PI): (project period 08/01/2017-31/07/2021). Role: Project PI.

NIH/NIAID R01 AI 117321 Attenuated HSV Vaccines that Induced Protective Mucosal Antibodies (B. Herold, W. Jacobs, G. Kelsoe multi-PI); (project period 3/1/2016 – 2/28/2020). Role: multi-PI.

NIH/NIAID UM1 AI 100645, Center for HIV/AIDS Vaccine Immunology - Immunogen Design (B.F. Haynes, PI) (project period: 01/07/12 - 06/31/2019). Role: project PI.

Bill and Melinda Gates Foundation Global Health Consortium Award OPP1111923, Nearest Neighbor Immunogen Strategies for HIV-1 (D. Baker, PI); (project period: 11/07/14-10/31/18). Role: project PI.

NIH/NIAID P01 AI 089618-05, Structure-function analysis of infection and vaccine induced B-Cell repertoires (S.C. Harrison, PI); (project period: 8/01/2014 – 07/31/2017). Role: core PI.

Quality Biological Inc. HHSN272201100023C Immunity to novel T/F SHIVs: variability in the co-evolution of virus and host immunity (G. Kelsoe, PI); (project period 12/01/2016-04/30/2017). Role: PI.

Bill and Melinda Gates Foundation, Protective Mucosal Antibodies Reponses to HIV-1 Envelope gp120 (B.F. Haynes, PI); (project period: 11/01/14-10/31/16). Role: Key personnel.

NIAID Contract HHSN272201000053C, Multiscale Systems Immunology (G. Kelsoe and T.B. Kepler, multi-PI); (project period: 09/30/2010-09/29/2015). Role: PI.

NIH/NIAID, P01 AI 089618, Structure-function Analysis of Infection- and Vaccine-induced B-cell Repertoires (S. Harrison, PI); (project period: 8/1/2014 - 7/31/2016). Role: core PI.

NIH-NIAID UM AI 109565, Immune Tolerance Network (G. Nepom, PI); (project period: 05/01/2015 – 01/31/2016). Culturing and isolating human B-cells using Athena technology. Role: project PI.

NIH/NIAID, U19 AI 91693, Eliciting B cells to produce anti-HIV gp41 MPER-specific neutralizing antibodies (E.L. Reinherz, PI) (project period: 09/01/10 - 08/31/2015). Role: project PI.

Bill and Melinda Gates Foundation Global Health Grant, Nearest neighbor Immunogen Strategies for HIV-1 (project period: 10/15/12 - 10/01/14). Role: PI.

Bill and Melinda Gates Foundation, Protective Mucosal Antibodies Reponses to HIV-1 Envelope gp120 (B.F. Haynes, PI); (project period: 09/12/11 - 9/11/14). Role: project PI.

(Research and training funds, *continued*)

NIH/NIAID R01 AI 81579, B Cell Tolerance and Humoral immunity to HIV-1 (project period: 08/01/09 - 07/31/13). Role: PI.

NIH/NIAID U19 AI 56363, Autoimmunity Center of Excellence, Modulation of B Cell Responses in Autoimmunity (E.W. St.Clair, PI); (project period: 06/01/04 – 05/31/14). Role: project PI.

NIH/NIAID U01 AI 67854, Center for HIV/AIDS Vaccine Immunology (B.F. Haynes, PI); (project period: 07/14/05 – 06/31/12). Role: project PI.

NIAID-R01 AI 24335, Analysis of the Murine Antibody Repertoire; (project period: 03/01/88 - 11/30/11). Role: PI.

Bill & Melinda Gates Foundation, Broadly Reactive Neutralizing Antibodies: Strategy for HIV Vaccine Design (B. Haynes, PI); (project period: 07/01/06 – 06/30/11). Role: project PI.

NIH/NIAID T32 AI 052077, Training Program in Basic Immunology;
(project period: 07/01/02 – 06/31/07). Role: PI.

NIH/NIAID R21 AI 058227, Microsimulation of Anthrax pathogenesis (T.B. Kepler, multi-PI); (project period: 7/1/2004-6/30/2006). Role: multi-PI.

NIH/NIAID R01 AI 49326, The role of complement in autoimmunity; (project period: 02/01/01 - 01/31/06). Role: PI.

Alliance for Lupus Research, Complement as a target for the treatment of lupus; (project period: 02/01/01 - 01/31/03). Role: PI.

NIH/NIA R01 AG 38950, Somatic Genetics of T cell Immunity; (project period: 02/01/96 - 01/31/01). Role: PI.

NIH/NIA PO1 AG 10207, Mechanisms of Immunosenesence; (project period: 04/01/92 - 09/30/00). Role: PI.

NIH/NIA RO1 AG 08192, Age's Immunological Consequences: Analysis of Clones; (project period: 07/01/88 - 06/30/92). Role: PI.

NSF DCB-8618289, Analysis of the Murine Antibody Repertoire; (project period: 05/15/87 - 03/01/88). Role: PI.

NIH/NCI Developmental Support Funds, CA 17701, Analysis of the Anti-Tumor and Autoimmune Paratopic Repertoire; (project period: 01/06/86 - 05/31/87). Role: PI.

NIH/NIAID R23 AI 20350, Regulatory Potential of Monoclonal Autochthonous Anti-Id; (project period: 07/01/83 - 06/30/86). Role: PI.

JOURNAL ARTICLES

1. **Kelsoe, G**., V. Allison and J.H. Martin. Electron microscopy of spermatogenesis in *Hymenolepis diminuta* (Cestoda). Tex. Rep. Biol. Med. *30*: 383-385; 1972.

2. **Kelsoe, G**., J. Ubelaker and V.F. Allison. The fine structure of spermatogenesis in *Hymenolepis diminuta* (Cestoda) with a description of the mature spermatozoon. Z. Parasitenk. *54*: 175-187; 1977.

3. **Kelsoe, G**. and J. Cerny. Regulation of the immune response. I. Regulatory cell equilibrium in the "virgin" state. Eur. J. Immunol. *8*: 176-180; 1978.

4. **Kelsoe, G**. and T.H. Weller. Immunodiagnosis of infection with *Schistosoma mansoni:* An ELISA method for the detection of antibody to circulating antigen. Proc. Natl. Acad. Sci. USA *75*: 5715-5717; 1978. (PMC393039)

5. Shadduck, J.A., **G. Kelsoe**, and R.J. Helmke. A microsporidan contaminant of a nonhuman primate cell culture: Ultrastructural comparison with *Nosema connori*. J. Parasitol. *65*: 185-188; 1979.

6. **Kelsoe, G**. and J. Cerny. Reciprocal expansions of idiotypic and anti-idiotypic clones following antigen stimulation. Nature (Lond.) *279*: 333-334; 1979.

7. **Kelsoe, G**., D. Issak and J. Cerny. Thymic requirement for cyclical idiotypic and reciprocal anti-idiotypic immune responses to a T-independent antigen. J. Exp. Med. *151*: 289-300; 1980.

8. **Kelsoe, G**., M. Reth and K. Rajewsky. Control of idiotope expression by monoclonal anti-idiotope antibodies. Immunol. Rev. *52:* 75-88; 1980.

9. Reth, M., **G. Kelsoe** and K. Rajewsky. Idiotypic regulation by isologous monoclonal anti-idiotope antibodies. Nature (Lond.) *290:* 257-259; 1981.

10. **Kelsoe, G**., M. Reth and K. Rajewsky. Control of idiotope expression by monoclonal anti-idiotope and idiotope-bearing antibody. Eur. J. Immunol. *11*: 418-423; 1981.

11. Sacks, D., **G. Kelsoe** and D. Sachs. Induction of immune responses with anti-idiotypic antibodies: Implications for the induction of protective immunity. Springer Seminars Immunopathol. *6*: 79-97; 1983.

12. **Kelsoe, G**. Network interactions, 1982: *Audivi, legi, fugi*. Surv. Immunol. Res. *2*: 230-232; 1983.

13. Beyreuther, K., J. Bovens, M. Bruggemann, R. Dildrop, **G. Kelsoe**, U. Krawinkel, C. Muller, S. Nishikawa, A. Radbruch, M. Reth, M. Siekevitz, T. Takemori, H. Tesch, G. Wildner, S. Zaiss and K. Rajewsky. Idiotypic determinants used in the analysis of antibody diversification and as regulatory targets. Annal. New York Acad. Sci. *418*: 121-129; 1984.

14. Cerny, J. and **G. Kelsoe**. Priority of the anti-idiotypic response after antigen administration: Artefact or intriguing network mechanism? Immunol. Today *5*: 61-63; 1984.

15. **Kelsoe, G**. Network Interactions, 1983. Surv. Immunol. Res. *3*: 169-171; 1984.

16. **Kelsoe, G**. Cloning of mitogen- and antigen-reactive B lymphocytes on filter paper discs. I. A description of the technique and of methods for the analysis of colonies. J. Immunol. Methods *76*: 345-363; 1985.

17. **Kelsoe, G**. Regulation of the immune response II. Concomitant idiotope-specific enhancement and suppression can result in a phenotypically normal response. Cell. Immunol. *98*: 145-155; 1986.

18. **Kelsoe, G**. and T. Stout. Cloning of mitogen- and antigen-reactive B lymphocytes on filter paper discs. II. Paratopic frequencies within the mitogen-selected repertoire. Cell. Immunol. *98*: 506-516; 1986.

19. Schulze, D. and **G. Kelsoe**. Genotypic analysis of B-cell colonies by *in situ* hybridization: stoichiometric expression of three V_H families in adult C57BL/6 and BALB/c mice. J. Exp. Med. *166*: 163-172; 1987.

20. **Kelsoe, G**. Cloning of mitogen- and antigen-reactive B lymphocytes on filter paper disks: phenotypic and genotypic analysis of B cell colonies. Methods Enzymol. *150*: 287-304; 1987.

21. **Kelsoe, G**., R. Miceli, J. Cerny, and D.H. Schulze. Mapping of antibody specificities to V_H gene families. Immunogenetics *29*: 288-296; 1989.

22. Kaushik, A., D.H. Schulze, C.A. Bona, and **G. Kelsoe**. Murine $V\kappa$ gene expression does not follow the V_H paradigm. J. Exp. Med. *169*: 1859-1864; 1989.

23. Striebich, C.C., R.M. Miceli, D.H. Schulze, **G. Kelsoe**, and J. Cerny. Antigen-binding repertoire and immunoglobulin heavy chain gene usage among B cell hybridomas from normal and autoimmune mice. J. Immunol. *144:* 857-1865; 1990.

24. Kaushik, A., D.H. Schulze, F.A. Bonilla, C.A. Bona, and **G. Kelsoe**. Stochastic pairing of heavy-chain and κ light-chain variable gene families occurs in polyclonally activated B cells. Proc. Natl. Acad. Sci. USA *87*: 4932-4936; 1990. (PMC54235)

25. Bona, C. A., Y. Saitoh, and **G. Kelsoe**. Pairing of V_H and $V\kappa$ gene families in self-reactive antibodies. J. Clin. Immunol. *10*: 223-236; 1990.

26. Sarzotti, M., V. Kumar, M. Bennett, and **G. Kelsoe**. Cloning of murine splenic T lymphocytes on filter paper discs: detection of a novel NK/T phenotype. Eur. J. Immunol. *21*: 635-641; 1991.

27. Kaushik, A., L. Reininger, **G. Kelsoe**, J.-C. Jaton and C. Bona. Contribution of the V_H 11 gene family to the mitogen responsive B cell repertoire in C57BL/6 mice. Eur. J. Immunol. *21*: 827-830; 1991.

28. **Kelsoe, G**. The primary antibody repertoire: the somatic genotype and paratopic phenotype of B-cell populations. Immunol. Series *55*: 81-92; 1991.

29. Jacob, J., R. Kassir and **G. Kelsoe**. *In situ* studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. I. The architecture and dynamics of responding cell populations. J. Exp. Med. *173*: 1165-1175; 1991.

30. Jacob, J., **G. Kelsoe**, K. Rajewsky and U. Weiss. Intraclonal generation of antibody mutants in germinal centres. Nature (Lond.) *354*: 389-392; 1991. [This publication reviewed in: MacLennan, I.C.M. The centre of hypermutation. Nature *354*: 352-353; 1991 and Nossal, G.J.V. The molecular and cellular basis of affinity maturation in the antibody response. Cell *68*: 1-2; 1992; Victora, G.D., Pinpointing the anatomical site of antibody affinity maturation. *Pillars of Immunology*, J Immunol *214*, 2025.]

31. Schulze, D.H., P. Mancillas, A. Kaushik, C. Bona and **G. Kelsoe**. Mitogen-induced V_H and $V\kappa$ expression is similar in young adult and aged mice. Aging: Immunol. Inf. Dis. *3*: 127-134; 1992.

32. Goidl, E.A., J. Cerny, **G. Kelsoe** and D.H. Schulze. Aging and humoral immunity. J. Maryland Med. Assn. *41*: 609-613; 1992.

33. Jacob, J. and **G. Kelsoe**. *In situ* studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. II. A common clonal origin for periarteriolar lymphoid sheath-associated foci and germinal centers. J. Exp. Med. *176*: 679-687; 1992.

34. Jacob, J., C. Miller and **G. Kelsoe**. *In situ* studies on the antigen-driven somatic hypermutation of immunoglobulin genes. Immunol. Cell Biol. *70*: 145-152; 1992.

35. **Kelsoe, G**. and B. Zheng. Sites of B-cell activation *in vivo*. Curr. Opin. Immunol. *5*: 418-422; 1993.

36. Yurovsky, V.V. and **G. Kelsoe**. Pairing of V_H gene families with the $\lambda 1$ light chain: evidence for a non-stochastic association. Eur. J. Immunol. *8*: 1975-1979; 1993.

37. Jacob, J., J. Przylepa, C. Miller, and **G. Kelsoe**. *In situ* studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. III. The kinetics of V-region mutation and selection in germinal center B cells. J. Exp. Med. *178*: 1293-1307; 1993. (PMC2191212)

38. **Kelsoe, G**. B cell diversification and differentiation in the periphery (Commentary). J. Exp. Med. *180*: 5-6; 1994.

39. Zheng, B., W. Xue, and **G. Kelsoe**. Locus-specific somatic hypermutation in germinal centre T cells. Nature (Lond.) *372*: 556-559; 1994.

40. Miller, C., **G. Kelsoe**, and S. Han. Lack of B7-2 expression in the germinal centers of aged mice. Aging: Immunol. Inf. Dis. 5: 249-258; 1994.

41. Kaushik, A., **G. Kelsoe**, and J.-C. Jaton. Nude mutation results in impaired primary antibody repertoire. Eur. J. Immunol. 25: 631-634; 1995.

42. Miller, C., J. Stedra, **G. Kelsoe**, and J. Cerny. Facultative role of germinal centers and T cells in the somatic diversification of IgV_H genes. J. Exp. Med. 181: 1319-1331; 1995.

43. Han, S., K. Hathcock, B. Zheng, T. Kepler, R. Hodes, and **G. Kelsoe**. Cellular interaction in germinal centers. The roles of CD40-ligand and B7-2 in established germinal centers. J. Immunol. *155*: 556-567; 1995.

44. **Kelsoe, G**., B. Zheng, and T. Kepler. Hypermutation in T cells questioned. A reply. (Scientific Correspondence). Nature (Lond.) *375*: 286; 1995.

45. **Kelsoe, G**. The germinal center reaction (Editorial). Immunol. Today 16: 324-326; 1995.

46. **Kelsoe, G**. In situ studies of the germinal center reaction. Adv. Immunol. 60: 267-288; 1995.

47. Miller, C. and **G. Kelsoe**. Immunoglobulin V_H hypermutation is absent in the germinal centers of aged mice. J. Immunol. 155: 3377-3384; 1995.

48. Han, S., B. Zheng, J. Dal Porto, and **G. Kelsoe**. In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. IV. Affinity-dependent, antigen-driven B cell apoptosis in germinal centers as a mechanism for maintaining self-tolerance. J. Exp. Med. 182: 1635-1644; 1995.

49. Saitoh, Y., **G. Kelsoe**, C. Bona, and A. Kaushik. Skewed V_H and $V\kappa$ gene family expression and pairing occurs among B lymphocytes in autoimmune motheaten mice. Autoimmunity. 21: 185-193; 1995.

50. Zheng, B., **G. Kelsoe**, and S. Han. Somatic diversification of antibody responses. J. Clin. Immunol. 16: 1-11; 1996.

51. **Kelsoe, G**. Life and death in germinal centers (redux). Immunity. *4*: 107-111; 1996. [Journal cover]

52. Croix, D.A., J.M. Ahearn, A.M. Rosengard, S. Han, **G. Kelsoe**, M. Ma, and M. C. Carroll. Antibody response to a T-dependent antigen requires B cell expression of complement receptors. J. Exp. Med. 1*83*: 1857-1864; 1996.

52. Wen, L., W. Pao, F.S. Wong, Q. Peng, J.E. Craft, B. Zheng, **G. Kelsoe**, M.J. Owen, and A.C. Hayday. Germinal center formation, immunoglobulin class switching, and autoantibody production driven by $\alpha\beta$ T cells. J. Exp. Med. *183*: 2271-2282; 1996.

53. Ferguson, S.E., S. Han, **G. Kelsoe**, and C.B. Thompson. CD28 is required for germinal center formation. J. Immunol. *156:* 4576-4581; 1996.

54. **Kelsoe, G**. The germinal center: a crucible for lymphocyte selection. Seminars Immunol. *8*: 179-184; 1996.

55. Fischer, M.B., M. Ma, S. Goerg, X. Zhou, J. Xia, O. Finco, S. Han, **G. Kelsoe**, T. Rothstein, E. Kummer, F.S. Rosen, and M. Carroll. Regulation of B cell responses to a T-dependent antigen by the classical pathway of complement. J. Immunol. *157*: 549-556; 1996.

56. Zheng, B., S. Han, and **G. Kelsoe**. T helper cells in murine germinal centers are antigen-specific emigrants that down-regulate Thy-1. J. Exp. Med. *184*: 1083-1091; 1996.

57. Pao, W., L. Wen, A.L. Smith, A. Gulbranson–Judge, B. Zheng, **G. Kelsoe**, I.C.M. MacLennan, M.J. Owen, and A.C. Hayday. γδ T cell help of B cells is induced by repeated parasitic infection, in the absence of other T cells. Curr. Biol. *10*: 1317–1325; 1996.

58. Zheng, B., S. Han, Q. Zhu, R. Goldsby, and **G. Kelsoe**. Alternative pathways for the antigen-specific selection of peripheral T cells. Nature (Lond.) *384*: 263-266; 1996. [Reviewed in: Metcalf, D. Another way to generate T cells? Nature Med. *3*: 18-19; 1997 and Tarlinton, D. Germinal centers: a second childhood for lymphocytes. Curr. Biol. *7*: R155-R159; 1997.]

59. Han, S., B. Zheng, D.G. Schatz, E. Spanopoulou, and **G. Kelsoe**. Neoteny in lymphocytes: Rag-1 and Rag-2 expression in germinal center B cells. Science (Wash. DC) *274*: 2094-2097; 1996. [Reviewed in: Tarlinton, D. Germinal centers: a second childhood for lymphocytes. Curr. Biol. *7*: R155-R159; 1997.]

60. Han, S., B. Zheng, Y. Takahashi, and **G. Kelsoe**. Distinctive characteristics of germinal center B cells. Semin. Immunol. *9*: 255-260; 1997.

61. Han, S., S.R. Dillon, B. Zheng, M.S. Schlissel, and **G. Kelsoe**. V(D)J recombinase activity in a subset of germinal center B lymphocytes. Science (Wash. DC) *278*: 301-305; 1997. [Reviewed in: Liu, Y.-J. Reuse of B lymphocytes in germinal centers. Science *278*: 238-239; 1997.]

62. Przylepa, J., C. Himes, and **G. Kelsoe**. Lymphocyte development and selection in germinal centers. Curr. Topics Microbiol. Immunol. *229*: 85-104; 1997.

63. Zheng, B., S. Han, Y. Takahashi, and **G. Kelsoe**. Immunosenesence and the germinal center reaction. Immunol. Rev. *160*: 63-77; 1997.

64. Takahashi, Y., P.R. Dutta, D.M. Cerasoli, and **G. Kelsoe**. In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl V. Affinity maturation develops in two stages of clonal selection. J. Exp. Med. *187*: 885-895; 1998. (PMC2212188)

65. Fischer, M.B., S. Goerg, L. Shen, C.C. Goodnow, **G. Kelsoe**, and M.C. Carroll. Survival of germinal center B cells is dependent on expression of CD21/CD35. Science (Wash. DC) *280*: 582-585; 1998.

66. **Kelsoe, G**. V(D)J hypermutation and DNA mismatch repair. Vexed by fixation. Proc. Natl. Acad. Sci. USA *95*: 6576-6577; 1998. (PMC33862)

67. Zheng, B., S. Han, E. Spanopoulou, and **G. Kelsoe**. Immunoglobulin gene hypermutation in germinal centers is independent of the RAG-1 V(D)J recombinase. Immunol. Rev. *162*: 133-141; 1998.

68. Radmacher, M.D., **G. Kelsoe**, and T.B. Kepler. Predicted and inferred waiting times for key mutations in the germinal center reaction: evidence for stochasticity in selection. Immunol. Cell Biol. *76:* 373-381; 1998.

69. Dal Porto, J., A. Haberman, M. Shlomchik, and **G. Kelsoe**. Antigen drives very low affinity B cells to become plasmacytes and enter germinal centers. J. Immunol. *161*: 5373-5381; 1998.

70. Yang, K., M. Davila, and **G. Kelsoe**. Do germinal centers have a role in the generation of lymphomas? Curr. Topics Microbiol. Immunol. *246*: 53-62; 1999.

71. **Kelsoe, G**. V(D)J hypermutation and receptor revision: coloring outside the lines. Curr. Opin. Immunol. *11*: 70-75; 1999.

72. Takahashi, Y., D.M. Cerasoli, J.M. Dal Porto, M. Shimoda, R. Freund, T.W. Behrens, and **G. Kelsoe**. Enforced expression of Bcl-x_L relaxes negative selection in germinal centers and impairs affinity maturation. J. Exp. Med. *190:* 399-410; 1999. (PMC195593)

73. Monroe, R.J., K. Seidl, F. Gaertner, S. Han, F. Chen, J. Sekiguchi, J. Wang, R. Ferrini, L. Davidson, **G. Kelsoe** and F.W. Alt. RAG2:GFP knock-in mice reveal novel aspects of RAG2 expression in primary and peripheral lymphoid tissues. Immunity. *11:* 201-212; 1999.

74. Langdon, S.D., M. Inaioki, **G. Kelsoe**, and T.F. Tedder. Germline sequences of VH7183 gene family members in C57BL/6 mice demonstrate natural selection of particular sequences during recent evolution. Immunogenetics *51*: 241-245; 2000.

75. Chen, Z., S.B. Koralov, M. Gendelman, M.C. Carroll, and **G. Kelsoe**. Humoral immune responses in $Cr2^{-/-}$ mice: Enhanced affinity maturation but impaired antibody persistence. J. Immunol. *164*: 4522-4532; 2000.

76. Chen, Z., S.B. Koralov, and **G. Kelsoe**. Regulation of humoral immune responses by CD21/CD35. Immunological Rev. *176*: 1-10; 2000.

77. Chen, Z., S.B. Koralov, and **G. Kelsoe**. Complement C4 inhibits systemic autoimmunity through a mechanism independent of complement receptors CR1 and CR2. J. Exp. Med. *192*: 1339-1352; 2000. (PMC2193358)

78. **Kelsoe, G**. Remembrance of things past. (News & Views.) Nature Immunol. *1*: 375-376; 2000.

79. **Kelsoe, G**. Studies of the humoral immune response. Immunol. Res. *22*: 199-210; 2000.

80. Cerasoli, D.M., **G. Kelsoe**, and M. Sarzotti. $CD4^+$ $Thy1^-$ thymocytes with a T_H - type 2 cytokine response. Intl. Immunol. *13*: 75-83; 2001.

81. Davila, M., S.J Foster, **G. Kelsoe**, and K. Yang. A role for illegitimate V(D)J recombination in peripheral B-lymphocytes in oncogenic chromosomal translocations? Adv. Cancer Res. *80*: 61-92; 2001.

82. Sandel, P.C., M. Gendelman, **G. Kelsoe**, and J.G. Monroe. Definition of a novel cellular constituent of the bone marrow that regulates the response of immature B cells to B-cell antigen receptor engagement. J. Immunol. *166*: 5935-5944; 2001.

83. Luzina, I.G., S.P. Atamas, C.E. Storrer, L.C. daSilva, **G. Kelsoe**, J.C. Papadimitriou, and B.S. Handwerger. Spontaneous formation of germinal centers in autoimmune mice. J. Leukocyte Biol. *70*: 578-584; 2001.

84. Dal Porto, J., A. Haberman, **G. Kelsoe**, and M. Shlomchik. Very low affinity B cells form germinal centers, become memory B cells, and participate in secondary immune responses when higher affinity competition is reduced. J. Exp. Med. *195*: 1215-1221; 2002. (PMC2193705)

85. Liang, H.-E., L.-Y. Hsu, D. Cado, L.G. Cowell, **G. Kelsoe**, and M.S. Schlissel. The "dispensable" portion of RAG-2 is necessary for efficient V-to-DJ rearrangement during B and T cell development. Immunity *17*: 639-651; 2002.

86. Cowell, L.G., M. Davila, T.B. Kepler, and **G. Kelsoe**. Identification and utilization of arbitrary correlations in models of recombination signal sequences. Genome Biology *3(12)*: research 0072.1-0072.20; 2002. (PMC151174)

87. Cowell, L., M. Davila, K. Yang, T.B. Kepler, and **G. Kelsoe**. Prospective estimation of recombination signal efficiency and identification of functional cryptic signals in the genome by statistical modeling. J. Exp. Med. *197*: 207-220; 2003. (PMC2193808)

88. Han, S., K. Yang, Z. Ozen, W. Peng, E. Marinova, **G. Kelsoe**, and B. Zheng. Enhanced differentiation of splenic plasma cells but diminished long-lived high-affinity bone marrow plasma cells in aged mice. J. Immunol. *170*: 1267-1273; 2003.

89. Lee, A.I., S.D. Fugmann, L.G. Cowell, L.M. Ptaszek, **G. Kelsoe**, and D.G. Schatz. A functional analysis of the spacer of V(D)J recombination signal sequences. PLoS Biol. *1*: 056-069; 2003. [*This was the first research article accepted for publication by* PLoS Biology. Accompanying *Primers* article: Markert, E. and Papavasiliou, N. V(D)J recombination and the evolution of the adaptive immune system. PLoS Biol. *1*: 024-027; 2003. (PMC212687).]

90. **Kelsoe, G**. Therapeutic CD154 antibody for lupus: a promise for the future? (Commentary) J. Clin. Invest. *112*: 1480-1482; 2003. (PMC259140).

91. Kincade, P.W., and **G. Kelsoe**. A birthday for B cells: Lymphopoiesis II, a scientific symposium honoring Max Cooper. (Commentary) Nat. Immunol. *4*: 1155-1157; 2003.

92. Sharov, A.A., Y. Piao, R. Matoba, D.B. Dudekula, Y. Qian, V. VanBuren, G. Falco, P.R. Martin, C.A. Stagg, U.C. Bassey, Y. Wang, M.G. Carter, T. Hamatani, K. Aiba, H. Akutsu, L. Sharova, T.S. Tanaka, W.L. Kimber, T. Yoshikawa, S.A. Jaradat, S. Pantano, R. Nagaraja, K.R. Boheler, D. Taub, D.L. Longo, D. Schlessinger, J. Keller, E. Klotz, **G. Kelsoe**, A. Umezawa, A.L. Vescovi, J. Rossant, T. Kunath, B.L.M. Hogan, A. Curci, M. D'Urso, J. Kelso, W. Hide, and M.S.H. Ko. Transcriptome analyses yield gene sets correlated with developmental potential in mouse stem cells and early embryos. PLoS Biol. *1*:410-419; 2003. (PMC300684).

93. Ueda, Y., K. Yang, S.J. Foster, M. Kondo, and **G. Kelsoe**. Inflammation controls B lymphopoiesis by regulating chemokine CXCL12 expression. J Exp Med. *199*: 47-58; 2004. (PMC1887733).

94. Gunn, M.D. and **G. Kelsoe**. Should we B-leavin' now? (News & Views). Nature Immunol. *5*: 703-704; 2004.

95. Cowell, L.G., M. Davila, D. Ramsden, and **G. Kelsoe**. Computational tools for understanding sequence variability in recombination signals. Immunol. Rev. *200*: 57-69; 2004. (PMC15242396).

96. Ueda, Y., M. Kondo, and **G. Kelsoe**. Inflammation and the reciprocal production of granulocytes and lymphocytes in bone marrow. J. Exp. Med. *201*: 1771-1780; 2005. (PMC1952536).

97. B.F. Haynes, M.A. Moody, L. Verkoczy, **G. Kelsoe**, and S.M. Alam. Antibody polyspecificity and neutralization of HIV-1: A hypothesis. Human Antibodies *14*: 59-67; 2005. (PMC2673565).

98. Holl, T.M. and **G. Kelsoe**. Outside influence: TLRs direct hematopoietic cell fates. Immunity *24*: 667-669; 2006. (PMC16782021).

99. Murray, J. M., J. P. O'Neill, T. Messier, J. Rivers, V. E. Walker, B. McGonagle, L. Trombley, L. Cowell, **G. Kelsoe**, F. McBlane, and B. A. Finette. V(D)J recombinase-mediated processing of coding junctions at cryptic recombination signal sequences in peripheral T-cells during human development. J Immunol *177*: 5393-5404; 2006. (PMC1937029).

100. Volkheimer, A.D., J. B. Weinberg, B. E. Beasley, J. F. Whitesides, J. P. Gockerman, J. O. Moore, **G. Kelsoe**, B. K. Goodman, and M. C. Levesque. Progressive immunoglobulin gene mutations in chronic lymphocytic leukemia: evidence for antigen-driven intraclonal diversification. Blood *109*: 1559-1567; 2007. (PMC1794047).

101. Ueda, Y., D. Liao, K. Yang, A. Patel, and **G. Kelsoe**. T-independent AID expression, class switch recombination, and antibody production by T1 B cells. J Immunol *178*: 3593–3601; 2007. (PMC1955467).

102. Alam, S.M., M. McAdams, D. Boren, M. Rak, R.M. Scearce, F. Gao; Z.T. Camacho, D. Gewirth, **G. Kelsoe**, P. Chen, B.F. Haynes. The role of antibody polyspecificity and lipid reactivity in binding of broadly neutralizing anti-HIV-1 envelope human monoclonal antibodies 2F5 and 4E10 to gp41 membrane proximal envelope epitopes. J Immunol *178*: 4424-4435; 2007. (PMC2262928).

103. Davila, M., F. Liu, L.G. Cowell, A.E. Lieberman, E. Heikamp, A. Patel, and **G. Kelsoe**. Multiple, conserved cryptic recombination signals in V_H gene segments: detection of cleavage products only in pro-B cells. J Exp Med *204*: 3195-3208; 2007. (PMC2150985).

104. DiLillo, D.J., Y. Hamaguchi, Y. Ueda, K. Yang, J. Uchida, K.M. Haas, **G. Kelsoe**, and T.F. Tedder. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. J Immunol, *180*: 361-371; 2008.

105. Cain, D., M. Kondo, H. Chen, and **G. Kelsoe**. Effects of Acute and Chronic Inflammation on B-Cell Development and Differentiation. J Invest Dermatol, *129*: 266-277; 2009. (PMC2778726).

106. Ueda, Y., D.W. Cain, M. Kuraoka, M. Kondo, and **G. Kelsoe**. IL-1RI dependent HSC proliferation is necessary for inflammatory granulopoiesis and reactive neutrophilia. J Immunol, *182*: 6477-6484; 2009. (PMC2780360).

107. Lieberman, A.E., M. Kuraoka, M. Davila, **G. Kelsoe**, and L.G. Cowell. Conserved cryptic recombination signals in Vκ gene segments are cleaved in pre-B cells. BMC Immunol, *10*:37-52; 2009. (PMC2711918).

108. Levesque, M.C., M.A. Moody, K.-K. Hwang, D.J. Marshall, J.F. Whitesides, J.D. Amos, T.C. Gurley, S. Allgood, B.B. Haynes, N.A. Vandergrift, S. Plonk, D.C. Parker, M.S. Cohen, G.D. Tomaras, P.A. Goepfert, G.M. Shaw, J.E. Schmitz, J.J. Eron, N.J. Shaheen, C.B. Hicks, H-X. Liao, M. Markowitz, **G. Kelsoe**, D.M. Margolis, and B.F. Haynes. B-cell polyclonal differentiation with gastrointestinal tract germinal center loss in the earliest stages of HIV-1 infection. PLoS Med, *6*: e1000107; 2009. (PMC2702159).

109. Bonsignori, M., M.A. Moody, R.J. Parks, T.M. Holl, **G. Kelsoe**, C.B. Hicks, N. Vandergrift, G.D. Tomaras, and B.F. Haynes. HIV-1 envelope induces memory B-cell responses that correlate with plasma antibody levels after gp120 protein vaccination or HIV-1 infection. J Immunol, *183*: 2708-2717; 2009. (PMC2767980).

110. Kuraoka, M., D. Liao, K. Yang, S.D. Allgood, M.C. Levesque, **G. Kelsoe**, and Y. Ueda. AID expression and activity in the absence of germinal centers: insights into hyper IgM syndrome. J Immunol, *183*: 3237-3248; 2009. (PMC2779701).

111. Verkoczy, L., M.A. Moody, T.M. Holl, H. Bouton-Verville, R. Scearce, J. Hutchinson, S.M. Alam, **G. Kelsoe**, and B.F. Haynes. Functional, non-clonal IgM^a-restricted B cell receptor interactions with the HIV-1 envelope gp41 membrane proximal external region. PLoS One, *4*: e7215; 2009. (PMC2751816).

112. Verkoczy, L., M. Diaz, T.M. Holl, Y. Ouyang, H. Bouton-Verville, S.M. Alam, M.A. Moody, L. Liao, **G. Kelsoe**, and B.F. Haynes. Immunological tolerance prevents the expression of a broadly reactive, protective HIV-1 antibody. Proc Natl Acad Sci USA, *107*: 181-186; 2010. (PMC2806760).

113. Holl, T.M., B.F. Haynes, and **G. Kelsoe**. Stromal cell-independent B-cell development *in vitro*: generation and recovery of 'forbidden' autoreactive clones. J Immunol Methods, *354*: 53-67; 2010. (PMC3835306). [Highlighted article for *J Immunol Methods* by Elsevier Press, 2010.]

114. Chen, H., D. Liao, I. McLeod, Z. Guan, D.W. Cain, Y. Ueda, P.B. Snowden, C. Raetz, and **G. Kelsoe**. Distinct granuloma responses in C57BL/6 and BALB/c mice in response to Pristane, Int J Exp Pathol, *91*: 460-471; 2010. (PMC2974958).

115. Holl, T.M., M.A. Moody, B.F. Haynes, and **G. Kelsoe**. B-cell development and differentiation during HIV infection: tolerance *versus* immunity. The Open Autoimmunity Journal *2*: 78-95; 2010. (PMC3835306).

116. Chen, H., D. Liao, T.M. Holl, P. Snowden, Y. Ueda, and **G. Kelsoe**. Genetic regulation of pristane-induced oil granuloma responses. Int J Exp Pathol, *91*: 472-483; 2010. (PMC3003845).

117. Nicely, N.I., S.M. Dennison, L. Spicer, R.M. Searce, **G. Kelsoe**, Y. Ueda, H. Chen, H.-X. Liao, S.M. Alam, and B.F. Haynes. Crystal structure of a non-neutralizing antibody to the HIV-1

gp41 membrane-proximal external region. Nature Struct Molec Biol *17*: 1492-1494; 2010. (PMID: 21076400).

118. **Kelsoe, G**. and D. Cain. A new guise for hyper-IgM syndrome. Blood *116*: 5785-5786; 2010. (PMID: 21183692).

119. Kuraoka, M., L. McWilliams, and **G. Kelsoe**. AID expression during B-cell development: searching for answers. Immunol Res *49*:3-13; 2011. (PMID: 21136202).

120. McGowan, P.O., T.A. Hope, W.H. Meck, **G. Kelsoe**, and C.L. Williams. Impaired social recognition memory in recombining gene 1-deficient mice. Brain Res *1383*: 187-195; 2011. (PMC3436067).

121. **Kelsoe, G**. B cell tolerance: Putting the horse before the cart. Arthritis Rheum *63*: 1173-1176; 2011. (PMID: 21538309).

122. Holl, E.K., B.P. O'Connor, T.M. Holl, K.E. Roney, A.G. Zimmermann, S. Jha, **G. Kelsoe**, and J. P.-Y. Ting. Plexin D1 is a novel regulator of germinal centers and humoral immune responses. J Immunol *186*: 5603-5611; 2011. (PMC3771081).

123. Cain, D.W., P.B. Snowden, G.D. Sempowski, and **G. Kelsoe**. Inflammation triggers emergency granulopoiesis through a density-dependent feedback mechanism. PLoS One *6*: e19957. doi:10.1371/journal.pone.0019957; 2011. (PMC3104996).

124. Verkoczy, L., **G. Kelsoe**, M.A. Moody, and B.F. Haynes. Role of immune mechanisms in induction of HIV-1 broadly neutralizing antibodies. Curr Opin Immunol *23*: 383-390; 2011. (PMC3139952).

125. Kuraoka, M., T.M. Holl, D. Liao, M. Womble, D. Cain, A.E. Reynolds, and **G. Kelsoe**. Activation-induced cytidine deaminase mediates central tolerance in B cells, Proc Natl Acad Sci USA 108: 11560-11565; 2011. (PMC3136303).

126. Bonsignori, M., K.-K. Hwang, X. Chen, C.-Y. Tsao, L. Morris, E. Gray, D.J. Marshall, J.A. Crump, S.H. Kapiga, N.E. Sam, F. Sinangil, M. Pancera, Y. Yongping, B. Zhang, J. Zhu, P.D. Kwong, S. O'Dell, J.R. Mascola, L. Wu, GJ. Nabel, S. Phogat, M.S. Seaman, J.F. Whitesides, M.A. Moody,**G. Kelsoe**, X. Yang, J. Sodroski, G.M. Shaw, D. Montefiori, T.B. Kepler, G.D. Tomaras, S.M. Alam, H.-X. Liao, and B.-F. Haynes. Analysis of a clonal lineage of HIV-1 envelope V2/V3 conformational epitope-specific, broadly neutralizing antibodies and their inferred, unmutated common ancestors, J Virol *85*: 9998-10009; 2011. (PMC3196428). ["Highly Cited Paper", *Essential Science Indicators*, Web of Science].

127. Verkoczy, L., Y. Chen, H. Bouton-Verville, J. Zhang, M. Diaz, J. Hutchinson, R.M. Scearce, Y.-B. Ouyang, S.M. Alam, T.M. Holl, K.-K. Hwang, **G. Kelsoe**, and B.F. Haynes. Rescue of HIV-1 broad neutralizing antibody-expressing B cells in 2F5 V_H/V_L knockin mice reveals multiple tolerance controls. J Immunol *187*: 3785-3797; 2011. (PMC3192533).

128. Alam, S.M., H.-X. Liao, S.M. Dennison, F. Jaeger, R. Parks, K. Anasti, A. Foulger, Michele Donathan, Judith Lucas, L. Verkoczy, N. Nicely, G.D. Tomaras, **G. Kelsoe**, B. Chen, T.B. Kepler, and B.F. Haynes. Differential reactivity of germline allelic variants of a broadly

neutralizing HIV-1 antibody to a gp41 fusion intermediate conformation, J Virol, *85*: 11725-11731; 2011. (PMC3209283).

129. Liao, H.-X., X. Chen, S. Munshaw, R. Zhang,D.J. Marshall, N. Vandergrift, J.F. Whitesides, X. Lu, J.-S. Yu, K.-K. Hwang, F. Gao, M. Markowitz, S.L. Heath, K.J. Bar, P. Goepfert, D. Montefiori, G. Shaw, M. Alam, D. Margolis, T.N. Denny, S.D. Boyd, E. Marshal, M. Egholm, B. Simen, B. Hanczaruk, A.Z. Fire, G. Voss, **G. Kelsoe**, G. Tomaras, M.A. Moody, T.B. Kepler, and B.F. Haynes. Initial antibodies binding to HIV-1 gp41 in acutely infected subjects are polyreactive and highly mutated. J Exp Med*, 208*: 2237-2249; 2011. (PMC3201211).

130. Moody, M.A., R. Zhuang, E.B. Walter Jr., C.W. Woods, G.S. Ginsburg, M.T. McClain, T.N. Denny, X. Chen, S. Munshaw, D.J. Marshall, J.F. Whitesides, M.S. Drinker, J.D. Amos, T.C. Gurley, J.A. Eudailey, A. Foulger, K.R. DeRosa, R. Parks, R.R. Meyerhoff, J.-S. Yu, D.M. Koznik, B.E. Barefoot, E.A. Ramsburg, S. Khurana, H. Golding, N.A. Vandergrift, S.M. Alam, G.D. Tomaras, T.B. Kepler, **G. Kelsoe**, H.-X. Liao, and B.F. Haynes. H3N2 influenza infection elicits more cross-reactive and less clonally expanded anti-hemagglutinin antibodies than influenza vaccination. PLoS One *6*: e25797; 2011. (PMC3198447).

131. Kuraoka, M. and **G. Kelsoe**. A novel role for activation-induced cytidine deaminase: central B-cell tolerance. Cell Cycle *10*: 3423-3424; 2011.

132. Haynes, B.F., **G. Kelsoe**, S.C. Harrison, and T.B. Kepler. B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. Nature Biotechnol *30*: 423–433; 2012. (PMC3512202). ["Highly Cited Paper", *Essential Science Indicators*, Web of Science].

133. Friedman, J., S.M. Alam, X. Shen, S.-M. Xia, S. Stewart, K. Anasti, J. Pollara, G. Yang, **G. Kelsoe**, G. Ferrari, G.D. Tomaras, B.F. Haynes, H.-X. Liao, M.A. Moody, and S.R. Permar. Isolation of HIV-1 neutralizing mucosal antibodies from colostrum. PLoS One *7*: e37684; 2012. (PMC3356285).

134. Moody, M.A., N.L. Yates, J.D. Amos, M.S. Drinker, J.A. Eudailey, T.C. Gurley, D.J. Marshall, J.F. Whitesides, X. Chen, A. Foulger, J.-S. Yu, R. Zhang, R.R. Meyerhoff, R. Parks, L. Wang, N.A. Vandergrift, J. Pickeral, J. Pollara, **G. Kelsoe**, S.M. Alam, G. Ferrari, D.C. Montefiori, G. Voss, H.-X. Liao, G.D. Tomaras, and B.F. Haynes. HIV-1 gp120 vaccine induces affinity maturation in both new and persistent antibody clonal lineages. J Virol *86*: 7496-7507; 2012. (PMC3416280).

135. Cain, D.W., S.E. Sanders, M.M. Cunningham, and **G. Kelsoe.** Disparate adjuvant properties among three formulations of alum. Vaccine *31*: 653-660; 2013. (PMC3541451).

136. Yang, G., T.M. Holl, Y. Liu, Y. Li, X. Lu, N.I. Nicely, T.B. Kepler, S.M. Alam, H.-X. Liao, D.W. Cain, L. Spicer, J.L. VandeBerg, B. F. Haynes, and **G. Kelsoe**. Identification of autoantigens recognized by the 2F5 and 4E10 broadly neutralizing HIV-1 antibodies. J Exp Med *120*: 241-256; 2013. (PMC3570098) [*Web of Science* "highly cited paper"; Journal cover].

137. Liao, H.-X., R. Lynch, T. Zhou, F. Gao, S.M. Alam, S.D. Boyd, A.Z. Fire, K.M. Roskin, C.A. Schramm, Z. Zhang, J. Zhu, L. Shapiro, NISC Comparative Sequencing Program, J.C. Mullikin, S. Gnanakaran, P. Hraber, K. Wiehe, **G. Kelsoe**, G. Yang, S.-M. Xia, D.C. Montefiori, R. Parks, K.E. Lloyd, R.M. Scearce, K.A. Soderberg, M. Cohen, G. Kaminga, M.K. Louder, L.M. Tran, Y. Chen, F. Cai, S. Chen, S. Moquin, X. Du, G.M. Joyce, S. Srivatsan, B. Zhang, A. Zheng, G.M. Shaw, B.H. Hahn, T.B. Kepler, B.T. Korber, P.D. Kwong, J.R. Mascola, and B.F.

Haynes. Co-evolution of a broadly HIV-1-neutralizing antibody and founder virus. Nature *496*: 469-476; 2013. [*Web of Science* "highly cited paper"; reviewed in *Nature* News, E.C. Hayden and News & Views, H. Mouquet and M.C. Nussenzweig; Nature 496: 441-442; 2013. *New England Journal of Medicine*, M. Ackerman and G. Alter, N Engl J Med 369: 389-391; 2013. *New York Times*, Donald G. McNeil, April 3, 2013. (PMC3637846)].

138. McWilliams, L., K.-Y. Su, X. Liang, D. Liao, S. Floyd, J. Amos, M.A. Moody, **G. Kelsoe**, and M. Kuraoka. CD27+ human developing B cells are enriched in fetal liver and exhibit characteristics of fetal lineage cells. J Leuk Biol *94*: 991-1001; 2013. (PMC3800071).

139. Kim, M., L. Song, J. Moon, Z.-Y. Sun, A. Bershteyn, M. Hanson, D. Cain, S. Goka, **G. Kelsoe**, G. Wagner, D. Irvine, and E.L. Reinherz. Immunogenicity of membrane-bound HIV-1 gp41 segments is dominated by residue accessibility and modulated by stereochemistry. J Biol Chem *288*:31888-31901; 2013. (PMC3814781).

140. Cain, D.W., E. O'Koren, M.J. Kan, M. Womble, G.D. Sempowski, M.D. Gunn, and **G. Kelsoe**. Identification of a tissue-specific, C/EBPβ-dependent pathway of differentiation for murine peritoneal macrophages. J Immunol *191*: 4665-4675; 2013. (PMC3808250).

141. **Kelsoe, G**., L. Verkoczy, and B.F. Haynes. Immune system regulation in the induction of broadly neutralizing HIV-1 antibodies. Vaccines *2*: 1-14; 2014. (PMC4053940).

142. Gearhart, P.J. and **G. Kelsoe**. A tribute to Michael S. Neuberger. (Obituary) J Clin Invest *124*: 3-5; 2014. (PMC3871264).

143. Holl, T.M., G. Yang, M. Kuraoka, L. Verkoczy, S.M. Alam, M.A. Moody, B.F. Haynes, and **G. Kelsoe**. Enhanced antibody responses to an HIV-1 MPER antigen in mice reconstituted with cultured lymphocytes. J Immunol *192*: 3269-3279; 2014. (PMC4003504).

144. Bonsignori, M., K. Wiehe, S.K. Grimm, R. Lynch, G. Yang, D.M. Kozink, F. Perrin, A. J. Cooper, K.-K. Hwang, X. Chen, M. Liu, K. McKee, R.J. Parks, J. Eudaley, M. Wang, M. Clowse, L.G. Criscione-Schreiber, M.A. Moody, M.E. Ackerman, S.D. Boyd, F. Gao, **G. Kelsoe**, L. Verkoczy, G.D. Tomaras, H.-X. Liao, T.B. Kepler, D.C. Montefiori, J.R. Mascola, and B.F. Haynes. An autoreactive antibody from an SLE/HIV-1 patient broadly neutralizes HIV-1. J Clin Invest *124*: 1835-1843; 2014. (PMC3973118).

145. Hwang, K.-K., A.M. Trama, D.M. Kozink, X. Chen, K. Wiehe, A.J. Cooper, S.-M. Xia, M. Wang, D.J. Marshall, J. Whitesides, S.M. Alam, G.D. Tomaras, S.L. Allen, K.R. Rai, J. McKeating, R. Catera, X.-J. Yan, C.C. Chu, **G. Kelsoe**, H.-X. Liao, N. Chiorazzi, and B.F. Haynes. IGHV1-69 B cell chronic lymphocytic leukemia antibodies cross-react with HIV-1 and hepatitis C virus antigens as well as intestinal commensal bacteria. PLoS One *10*: e90725; 2014. (PMC3948690).

146. Caro-Maldonado, A., R. Wang, A.G. Nichols, M. Kuraoka, A.L. Gavin, **G. Kelsoe**, D.R. Green, and J.C. Rathmell. B-cell activation broadly regulates metabolism and glycolytic flux in anergy and antibody production. J Immunol *192*:3626-3636; 2014. (PMC3984038).

147. Kepler, T.B., K.J. Wiehe, S. Munshaw, C.W. Woods, T.N. Denny, G.D. Tomaras, S.M. Alam, M.A. Moody, **G. Kelsoe**, H.-X. Liao, and B.F. Haynes. Reconstructing a B-cell Clonal Lineage. II. Mutation, Selection, and Affinity Maturation. Frontiers Immunol *5*: 705; 2014. (PMC4001017).

148. Verkoczy, L., **G. Kelsoe**, and B.F. Haynes. HIV-1 envelope gp41 broadly neutralizing antibodies: hurdles for vaccine development. PLoS Pathog *10*: e1004037; 2014. (PMC4031215).

149. Haynes, B.F., L. Verkoczy, and **G. Kelsoe**. Redemption of Autoreactive B Cells. Proc Natl Acad Sci USA *111*: 9022-9023; 2014. (PMC4078812).

150. Gao, F., M. Bonsignori, H.-X. Liao, A. Kumar, S.-M. Xia, X. Lu, F. Cai¸ K.-K. Hwang, H. Song, T. Zhou, R.M. Lynch, S.M. Alam, M.A. Moody, G. Ferrari, M. Berrong, **G. Kelsoe**, G.M. Shaw, B.H. Hahn, L. Morris, D.C. Montefiori, G. Kamanga, M. Cohen, P. Hraber, P.D. Kwong, B.T. Korber, J.R. Mascola, T.B. Kepler, and B.F. Haynes. Cooperation of B cell lineages in induction of HIV-1 broadly neutralizing antibodies. Cell *158*: 481-491; 2014. (PMC4150607). [Reviewed in M.G. McHeyzer-Williams Cell *158*: 475-476; 2014.]

151. Haynes, B.F, M.A. Moody, S.M. Alam, M. Bonsignori, L. Verkoczy, G. Ferrari, F. Gao, G.D. Tomaras, H.-X. Liao and **G. Kelsoe**. Progress in HIV-1 vaccine development. J Allergy Clin Immunol *134*: 3-10; 2014. (PMC4133697).

152. Kepler, T.B., H.-X. Liao, S.M. Alam, R. Bhaskarabhatla, R. Zhang, S. Stewart, K. Anasti, **G. Kelsoe**, R. Parks, K.E. Lloyd, C. Stolarchuk, J. Pritchett, E. Solomon, E. Friberg, L. Morris, S.S.A. Karim, M.S. Cohen, E. Walter, M.A. Moody, X. Wu, H.R. Altae-Tran, I.S. Georgiev, P.D. Kwong, S.D. Boyd, A.Z. Fire, J.R. Mascola, B.F. Haynes. Immunoglobulin gene insertions and deletions in the affinity maturation of HIV-1 broadly reactive neutralizing antibodies. Cell Host Microbe *16*: 304-313; 2014. (PMC4163498).

153. **Kelsoe, G**. Curiouser and curiouser: The role(s) of AID expression in self-tolerance. Eur J Immunol *44*: 2876-2879; 2014.

154. Wiehe, K., D. Easterhoff, K. Luo, N. Nicely, T. Bradley, F.H. Jaeger, S.M. Dennison, R. Zhang, K.E. Lloyd, C. Stolarchuk, R. Parks, L.L. Sutherland, R.M. Scearce, L. Morris, J. Kaewkungwal, S. Nitayaphan, P. Pitisuttithum, S. Rerks-Ngarm, N. Michael, J. Kim, **G. Kelsoe**, D.C. Montefiori, G. Tomaras, M. Bonsignori, S. Santra, T.B. Kepler, S.M. Alam, M.A. Moody, H.-X. Liao, and B.F. Haynes. Antibody light-chain-restricted recognition of the site of immune pressure in the RV144 HIV-1 vaccine trial is phylogenetically conserved. Immunity *41*:909-918; 2014. (PMC4324565).

155. Liu, M., G. Yang, K. Wiehe, N.I. Nicely, M. Bonsignori, S.M. Alam, J. Gao, B.F. Haynes, and **G. Kelsoe**. Autoreactivity and polyreactivity among HIV-1 antibodies. J Virol *89*: 784-798; 2015. (PMC4301171). ["Highly Cited Paper", *Essential Science Indicators*, Web of Science]

156. Reynolds, A.E., M. Kuraoka, and **G. Kelsoe**. Natural IgM is produced by CD5- plasma cells that occupy a distinct survival niche in bone marrow. J Immunol *194*: 231-242; 2015. (PMC4272881)

157. **Kelsoe, G**. Heavy-Chain Receptor Editing Unbound. Proc Natl Acad Sci USA *112*: 2297-2298; 2015. (PMC4345620).

158. Ci, X., M. Kuraoka, H. Wang, Z. Carico, K. Hopper, J. Shin, X. Deng, Y. Qiu, S. Unniraman, **G. Kelsoe**, and X.-P. Zhong. TSC1 promotes B cell maturation but is dispensable for germinal center formation. PLoS One: 10, doi: 10.1371/journal.pone.0127527; 2015. (PMC4441391).

159. Bradley, T., D. Fera, J. Bhiman, L. Eslamizar, X. Lu, K. Anasti, R. Zhang, L.L. Sutherland, R.M. Scearce, C. Stolarchuk, K.E. Lloyd, R. Parks, A. Martelli, A. Foulger, X. Nie, S.S. Abdool-Karim, S. Barnett, **G. Kelsoe**, T.B. Kepler, S.M. Alam, D.C. Montefiori, M.A. Moody, H.-X. Liao, L. Morris, S. Santra, S.C. Harrison, and B.F. Haynes. Structural constraints of vaccine-induced tier-2 autologous HIV neutralizing antibodies: targeting the receptor binding site. Cell Reports *14*: 43-54, 2016. (PMC4706810).

160. Haynes, B.F., G.M. Shaw, B.T. Korber, **G. Kelsoe**, J. Sodroski, B.H. Hahn, P. Borrow, and A.J. McMichael. HIV-host interactions: implications for vaccine development. Cell Host Microbe *19*: 292-303; 2016. (PMC4823811). ["Highly Cited Paper", *Essential Science Indicators*, Web of Science].

161. Kuraoka, M., A.G. Schmidt, T. Nojima, F. Feng, D. Kitamura, S.C. Harrison, T.B. Kepler, and **G. Kelsoe**. Complex antigens drive permissive clonal selection in germinal centers. Immunity *44*: 542-552; 2016. (PMC4794380). [Reviewed in K. Neu and P.C. Wilson. Immunity *44*: 518-520; 2016].

162. Bonsignori, M., T. Zhou, Z. Sheng, L. Chen, F. Gao, M.G. Joyce, G. Ozorowski, G.-Y. Chuang, C.A. Schramm, K. Wiehe, S.M. Alam, T. Bradley, M. Gladden, K.-K. Hwang, S. Iyengar, A. Kumar, X. Lu, K. Luo, M.C. Mangiapani, R.J. Parks, H. Song, P. Acharya, R.T. Bailer, A. Cao, A. Druz, I.S. Georgiev, Y.D. Kwon, M.K. Louder, B. Zhang, A. Zheng, B.J. Hill, R. Kong, C. Soto, NISC Comparative Sequencing Program, J.C. Mullikin, D.C. Douek, D.C. Montefiori, M.A. Moody, G.M. Shaw, B.H. Hahn, **G. Kelsoe**, P. T. Hraber, B.T. Korber, S.D. Boyd, A.Z. Fire, T.B. Kepler, L. Shapiro, A.B. Ward, J.R. Mascola, H.-X. Liao, P.D.Kwong, and B.F. Haynes. Maturation pathway from germline to broad HIV-1 neutralizer of a CD4-mimic antibody. Cell *165*: 449-463; 2016. (PMC4826291). ["Highly Cited Paper", *Essential Science Indicators*, Web of Science].

163. Zhang, R., L. Verkoczy, K. Wiehe, S.M. Alam, N.I. Nicely, S. Santra, T. Bradley, C.W. Pemble, J. Zhang, F. Gao, D.C. Montefiori, H. Bouton-Verville, **G. Kelsoe**, K. Larimore, P.D. Greenberg, R. Parks, A. Foulger, J.N. Peel, K. Luo, X. Lu, A.M. Trama, N. Vandergrift, G.D. Tomaras, T.B. Kepler, M.A. Moody, H.-X. Liao, and B.F. Haynes. Initiation of HIV envelope gp41 neutralizing B cell lineages. Science Transl Med *8*: 336ra62; 2016. (PMC5006673).

164. Moody, M.A., I. Pedroza-Pacheco, N.A. Vandergrift, C. Chui, K.E. Lloyd, R. Parks, K.A. Soderberg, A.T. Ogbe, M.S. Cohen, H.-X. Liao, F. Gao, A.J. McMichael, D.C. Montefiori, L. Verkoczy, **G. Kelsoe**, J. Huang, P.R. Shea, M. Connors, P. Borrow, and B.F. Haynes. Immune perturbations in HIV-1-infected individuals who make broadly reactive neutralizing antibodies, Science Immunol *1*: aag0851; 2016.

165. Khandelwal, S., G.M. Lee, C.G. Hester, M. Poncz, S. McKenzie, B. Sachais, L. Rauova L. Rauova, **G. Kelsoe**, D.B Cines, M. Frank, G.M. Arepally. The antigenic complex in HIT binds

to B-cells via complement and complement receptor 2 (CD21). Blood *128*: 1789-1799; 2016. (PMC5054694). [Plenary Paper; Reviewed in T.E. Warkentin. Blood *128*:1781-1782; 2016.]

166. Abbott, R.K., M. Thayer, J. Labuda, M. Silva, P. Phillbrook, D.W. Cain, H. Kojima, S. Hatfield, S. Sethumadhavan, A. Ohta, E.L. Reinherz, **G. Kelsoe**, and M. Sitkovsky. Germinal center hypoxia potentiates immunoglobulin class switch recombination. J Immunol *197*:4014-4020; 2016. (PMC5123804).

167. Su, K.-Y., M. Kuraoka, A. Watanabe, and **G. Kelsoe**. Efficient culture of human naïve and memory B cells for use as antigen-presenting cells. J Immunol *197*: 4163-4176; 2016. (PMC5111638).

168. van Gils, M.J., T.L. van den Kerkhof, G. Ozorowski, C.A. Cottrell, D. Sok, M. Pauthner, J. Pallesen, N. de Val, A. Yasmeen, S.W. de Taeye, A. Schorcht, S. Gumbs, I.Johanna, K. Saye-Francisco, C.-H. Liang, E. Landais, X. Nie,L.K. Pritchard, M. Crispin, **G. Kelsoe**, I.A. Wilson, H. Schuitemaker, P.J. Klasse, J.P. Moore, D.R. Burton, A.B. Ward, and R.W. Sanders. An HIV-1 antibody from an elite neutralizer implicates the fusion peptide as a site of vulnerability. Nature Microbiol *2*: 16199,10.1038/nmicrobiol.2016.199; 2016. (PMC5372380). [“Highly Cited Paper”, *Essential Science Indicators*, Web of Science].

169. Bradley, T., G. Yang, O. Ilkayeva , T.M. Holl, R. Zhang, J. Zhang, S. Santra, C.B. Fox, S.G. Reed, R. Parks, C.M. Bowman, H. Bouton-Verville, L.L. Sutherland, R.M. Scearce, N. Vandergrift ,T.B. Kepler, M.A. Moody, H.-X. Liao, S.M. Alam, R. McLendon, J.I. Everitt, C.B. Newgard, L. Verkoczy, **G. Kelsoe**, and B.F. Haynes. HIV-1 envelope mimicry of host enzyme kynureninase does not disrupt tryptophan metabolism. J Immunol *197*: 4463-4673; 2016. (PMC5111638).

170. Huang, J., B.H. Kang, E. Ishida, T. Zhou, T. Griesman, Z. Sheng, F. Wu, N.A. Doria-Rose, B. Zhang, K. McKee, S. O’Dell, G.-Y. Chuang, A. Druz, I.S. Georgiev, C.A. Schramm, A. Zheng, M.G. Joyce, M. Asokan, A. Ransier, S. Darko, M.S. Migueles, R.T. Bailer, M.K. Louder, S.M. Alam, R. Parks, **G. Kelsoe**, T. Von Holle, B.F. Haynes, D.C. Douek, V. Hirsch, M.S. Seaman, L. Shapiro, J.R. Mascola, P.D. Kwong, and M. Connors. Identification of a CD4-binding-site antibody to HIV that evolved near-pan neutralization breadth. Immunity *45*: 1108-1121; 2016. (PMC5770152). [Reviewed in D. Sok and D.R. Burton. Immunity *45*:958-960; 2016.]

171. **Kelsoe, G**. and B.F. Haynes. Host controls of HIV broadly neutralizing antibody development. Immunol Rev *275*: 79-88; 2017. (PMC5479487).

172. Kuraoka, M., P.B. Snowden, T. Nojima, L. Verkoczy, B.F. Haynes, D. Kitamura, and **G. Kelsoe**. BCR and endosomal TLR signals synergize to increase AID expression and establish central B-cell tolerance. Cell Reports *18*: 1627-1635; 2017. (PMC5328188).

173. Bonsignori, M., E.F. Kreider, D. Fera, R.R. Meyerhoff, T. Bradley, K. Wiehe, S.M. Alam, K.-K. Hwang, K.O. Saunders, R. Zhang, M.A. Gladden, A. Monroe, A. Kumar, S.-M. Xia, M. Cooper, M.K. Louder, K. McKee, R.T. Bailer, B.W. Pier, C.A. Jette, **G. Kelsoe**, W.B. Williams, L. Morris, J. Kappes, K. Wagh, G. Kamanga, M.S. Cohen, P.T. Hraber, D.C. Montefiori, A. Trama, H.-X. Liao, T.B. Kepler, M.A. Moody, F. Gao, J.R. Mascola, G.M. Shaw, B.H. Hahn, S.C.

Harrison, B.T. Korber, and B.F. Haynes. Staged induction of HIV-1 glycan-dependent broadly neutralizing antibodies. Sci Transl Med *9*: eaai7514; 2017. (PMC5562350).

174. Takahashi, Y. and **G. Kelsoe**. Memory B-cells respond to viral evolution by permissive selection in germinal centers. Curr Opinion Immunol *45*:119-125; 2017. (PMC5449227).

175. Wiehe, K., N.I. Nicely, B. Lockwood, M. Kuraoka, K. Anasti, S. Arora, C.M. Bowman, C. Stolarchuk, R. Parks, K.E. Lloyd, S.M. Xia, R. Duffy, X. Shen, C.A. Kyartsous, L.E. MacDonald, A.J. Murphy, R.M. Scearce, M.A. Moody, S.M. Alam, L. Verkoczy, G.D. Tomaras, **G. Kelsoe**, B.F. Haynes. Immunodominance of antibody recognition of the HIV envelope V2 region in Ig-humanized mice. J Immunol *198*: 1047-1055; 2017. (PMC5262538).

176. Williams, L.D., G. Ofek, S. Schätzle, J.R. McDaniel, X. Lu, N.I. Nicely, L. Wu, C. Lougheed, T. Bradley, M.K. Louder, K. McKee, R.T. Bailer, S. O'Dell, I.S. Georgiev, M.S. Seaman, R.J. Parks, D.J. Marshall, K. Anasti, G. Yang, X. Nie, N.L. Tumba, K. Wiehe, K. Wagh, B. Korber, T.B. Kepler, S.M. Alam, L. Morris, G. Kamanga, M.S. Cohen, M. Bonsignori, S.-M. Xia, D.C. Montefiori, **G. Kelsoe**, F. Gao, J.R. Mascola, M.A. Moody, K.O. Saunders, H.-X. Liao, G.D. Tomaras, G. Georgiou, and B.F. Haynes. Potent and broad HIV-neutralizing antibodies in memory B cells and plasma. Sci Immunol *2*(7). pii: eaal2200; 2017. (PMC5905719).

177. Williams, W.B., J. Zhang, C. Jiang, N.I. Nicely, D. Fera, K. Luo, M.A. Moody, H.-X. Liao, S.M. Alam, T. Kepler, A. R., K. Wiehe, J.A. Holland, T. Bradley, N. Vandergrift, K.O. Saunders, R. Parks, A. Foulger, S.-M. Xia, D.C. Montefiori, M. Louder, A. Eaton, S. Santra, R. Scearce, L. Sutherland, A. Newman, H. Bouton-Verville, C. Bowman, H. Bomze, F. Gao, D.J. Marshall, J.F. Whitesides, X. Nie, **G. Kelsoe**, S.G. Reed, C.B. Fox, K. Clary, M. Koutsoukos, D. Franco, J.R. Mascola, S.C. Harrison, B.F. Haynes, and L. Verkoczy. Initiation of HIV neutralizing B cell lineages with sequential envelope immunizations. Nat Commun *8*(1):1732. doi: 10.1038/s41467-017-01336-3; 2017. (PMC5701043).

178. Silva, M., T.H. Nguyen, P. Philbrook, M. Chu, O. Sears, S. Hatfield, R.K. Abbott, **G. Kelsoe**, and M.V. Sitkovsky. Targeted elimination of immunodominant B cells drives the germinal center reaction toward subdominant epitopes. Cell Reports *21*: 3672-3680; 2017. doi: 10.1016/j.celrep.2017.12.014. (PMC5771444).

179. McCarthy, K., A. Watanabe, M. Kuraoka, G. Bajic, K.T. Do, A.G. Schmidt, **G. Kelsoe**, and S.C. Harrison. Human memory B cells that crossreact with group 1 and group 2 influenza A viruses are abundant in adult human repertoires. Immunity *48*: 174-184; 2018. (PMC5810956). ["Highly Cited Paper", *Essential Science Indicators*, Web of Science].

180. Yeh, C.-H., T. Nojima, M. Kuraoka, and **G. Kelsoe**. Germinal center entry not selection of B cells is controlled by peptide-MHCII complex density. Nat Commun. *9*: *article no*. 928; 2018. doi: 10.1038/s41467-018-03382-x. (PMC5834622).

181. Finney, J., C.-H. Yeh, **G. Kelsoe**, and M. Kuraoka. Germinal center responses to complex antigens. Immunol Rev *284*: 42-50; 2018. (PMC6023402).

182. Finney, J. and **G. Kelsoe**. Poly- and autoreactivity of HIV-1 bNAbs: Implications for vaccine design. Retrovirol *15*: 53-60; 2018. (PMC6064052).

183. Kuraoka, M., E. Meffre, and **G. Kelsoe**. The first tolerance checkpoint in mice and humans: control by AID. Adv Immunol *139*: 51-92; 2018.

184. Bonsignori, M., E. Scott, K. Wiehe, D. Easterhoff, S.M. Alam, K.K. Hwang, M. Cooper, S.-M. Xia, R. Zhang, D.C. Montefiori, R. Henderson, X. Nie, **G. Kelsoe**, M.A. Moody, X. Chen, M.G. Joyce, P.D. Kwong, M. Connors, J. Mascola, A.T. McGuire, L. Stamatatos, M. Medina-Ramírez, R.W. Sanders, K.O. Saunders, T.B. Kepler, B.F. Haynes. Dual maturation pathways from the unmutated common ancestor of HIV-1 envelope broadly neutralizing antibodies overcome glycan barriers. Immunity *49*: 1162-1174; 2018. (PMC6303191).

185. Bajic, G., C.E. van der Poel, M. Kuraoka, A.G. Schmidt, M.C. Carroll, **G. Kelsoe**, and S.C. Harrison. Autoreactivity profiles of influenza hemagglutinin broadly neutralizing antibodies. Sci Rep *9*: *article no.* 3492; 2019. doi.org/10.1038/s41598-019-40175-8. (PMC6401307).

186. Watanabe, A., K.-Y. Su, M. Kuraoka, G. Yang, A.E. Reynolds, A.G. Schmidt, S.C. Harrison, B.F. Haynes, E.W. St. Clair, and **G. Kelsoe**. Self-tolerance significantly reduces the B-cell repertoire to microbial epitopes. JCI Insight *4*(10), 2019:e122551. (PMC6542615). (doi.org/10.1172/jci.insight.122551. [Noted in *JCI This Month*, June 2019.]

187. Watanabe, A., K.R. McCarthy, M. Kuraoka, A.G. Schmidt, Y. Adachi, T. Onodera, K. Tonouchi, T.M. Caradonna, G. Bajic, S. Song, C.E. McGee, G.D. Sempowski, F. Feng, P. Urick, T.B. Kepler, Y.Takahashi, S.C. Harrison, and **G. Kelsoe**. Antibodies to a conserved Influenza head-interface epitope protect by an IgG subtype dependent mechanism. Cell: *177*: 1124–1135; 2019. (PMC6825805). [Reviewed in Y. Wu and G.F. Gao. “Breathing’’ hemagglutinin reveals cryptic epitopes for universal influenza vaccine design. Cell *177*: 1086-1087; 2019.]

188. Bajic, G., M.J. Maron, Y. Adachi, T. Onodera, Y. Takahashi, **G. Kelsoe**, M. Kuraoka, and A.G. Schmidt. Immune focusing to a broadly protective subdominant viral epitope by antigen engineering. Cell Host & Microbe *25*: 827-835; 2019. doi.org/10.1016/j.chom.2019.04.003. (PMC6748655). [Reviewed in Y. Wu and G.F. Gao. “Breathing’’ hemagglutinin reveals cryptic epitopes for universal influenza vaccine design. Cell *177*: 1086-1087; 2019.]

189. Adachi, Y., K. Tonouchi, A. Nithichanon, M. Kuraoka, A. Watanabe, R. Shinnakasu, H. Asanuma, A. Ainai, Y. Ohmi, T. Yamamoto, K. Ishii, H. Hasegawa, H. Takeyama, G. Lertmemongkolchai, T. Kurosaki, M. Ato, **G. Kelsoe**, and Y. Takahashi. Exposure of occluded hemagglutinin epitope drives the selection of a class of cross-protective influenza antibodies. Nature Comm, *10*: article no. 3883; 2019. doi.org/10.1038/s41467-019-11821-6. (PMC6713747).

190. Finney, J., A. Watanabe, **G. Kelsoe**, and M. Kuraoka. Minding the gap: the impact of B-cell tolerance on the microbial antibody repertoire. Immunol Rev. *292*: 24-36; 2019. doi: 10.1111/imr.12805. (PMC6023402).

191. Onodera, T., R.K. Shukla, M. Miki, R. Todaka, M. Kuraoka, H. Hasegawa, M. Ato, **G. Kelsoe**, K. Katayama, and Y. Takahashi. Virus particulate structure permits selective elicitation of protective IgA responses. J Immunol. *203*: 3282-3292; 2019. doi: 10.4049/jimmunol.1900481. (PMC6900486).

192. Finney, J., G. Yang, M. Kuraoka, T. Nojima, L. Verkoczy, D. Kitamura, B.F. Haynes, and **G. Kelsoe**. Cross-reactivity to kynureninase tolerizes B cells that express the HIV-1 broadly

neutralizing antibody 2F5. J Immunol *203*: 3268-3281; 2019. doi: 10.4049/jimmunol.1900069. (PMC6904439).

193. Bajic, G., M.J. Maron, T.M. Caradonna, M. Tian, A. Mermelstein, D. Fera, **G. Kelsoe**, M. Kuraoka, and A.G. Schmidt. Structure-guided molecular grafting of a complex broadly neutralizing viral epitope. ACS Infect Dis *6*: 1182-1191; 2020. doi: 10.1021/acsinfecdis.0c00008. (PMC7291361).

194. Bradley, T., M. Kuraoka, C.-H. Yeh, M. Tian, H. Chen, D. Cain, X. Chen, A. Ellebedy, R. Parks, M. Barr, L.L. Sutherland, R.M. Scearce, C.M. Bowman, H. Bouton-Verville, S. Santra, K. Wiehe, D. Montefiori, M. Bonsignori, M.A. Moody, L. Verkoczy, K.O. Saunders, R. Ahmed, J.R. Mascola, **G. Kelsoe**, F.W. Alt, and B.F. Haynes. Immune checkpoint modulation enhances HIV-1 antibody induction. Immune checkpoint modulation enhances HIV-1 antibody induction. *Nat Commun 11***,** 948; 2020. https://doi.org/10.1038/s41467-020-14670-w. (PMC7031230).

195. Nojima, T., A.E. Reynolds, D. Kitamura, **G. Kelsoe**, and M. Kuraoka. Tracing self-reactive B cells in normal mice. J Immunol *205*: 90-101; 2020. (PMC7311292).

196. Finney, J. and **G. Kelsoe**. Ideal vaccines: balancing B-cell recruitment and differentiation. Immunity *53*: 473-475; 2020. doi: 10.1016/j.immuni.2020.08.008.

197. Roark, R.S., L. Hui Li, W.B. Williams, H. Chug, R.D. Mason, J. Gorman, S. Wang, F.H. Lee, J. Rando, M. Bonsignori, K.O. Saunders, K. Wiehe, M.A. Moody, P.T. Hraber, K. Wagh, E.E. Giorgi, R.M. Russell, F. Bibollet-Ruche, W. Liu, A. Connell, A.G. Smith, J. DeVoto, A.I. Murphy, J. Smith, W. Ding, C. Zhao, N. Chohan, M. Okumura, C. Rosario, Y. Ding, E. Lindemuth, A.M. Bauer, K.J. Bar, D. Ambrozak, C. Chao, G.Y. Chuang, H. Geng, C.L. Lin, M.K. Louder, R. Nguyen, B. Zhang, D. Raymond, K.K. Hwang, N.A. Doria-Rose, C.A. Schramm, D.C. Douek, M. Roederer, T.B. Kepler, **G. Kelsoe**, J.R. Mascola, P.D. Kwong, B.T. Korber, S.C. Harrison, B.F. Haynes, B.H. Hahn, and G.M. Shaw. Recapitulation of HIV-1 Env-antibody coevolution in macaques leading to neutralization breadth. Science *371*(6525): eabd2638; 2021. doi: 10.1126/science.abd2638. (PMC8040783).

198. Williams, W.B., R. Meyerhoff, R.J. Edwards, H. Li, N.I. Nicely, R. Henderson, Y. Zhou, K. Janowska, K. Mansouri, K. Manne, V. Stalls, A.L. Hsu, M.J. Borgnia, G. Stewart-Jones, M.S. Lee, N. Bronkema, J. Perfect, M.A. Moody, K. Wiehe, T. Bradley, T.B. Kepler, S.M. Alam, R.J. Parks, A. Foulger, M. Bonsignori, C.C. LaBranche, D.C. Montefiori, M. Seaman, S. Santra, J.R. Francica, G.M. Lynn, B. Aussedat, W.E. Walkowicz, R. Laga, **G. Kelsoe**, K.O. Saunders, D. Fera, P.D. Kwong, R. Seder, A. Bartesaghi, G.M. Shaw, P. Acharya, and B.F. Haynes. Fab-dimerized glycan-reactive antibodies neutralize HIV and are prevalent in humans and rhesus macaques. Cell *184*: 2955-2972; 2021. doi: 10.1016/j.cell.2021.04.042. (PMC8135257).

199. McCarthy, K.R., J. Lee, A. Watanabe, M. Kuraoka, L.R. Robinson-McCarthy, G. Georgiou, **G. Kelsoe**, and S.C. Harrison. A prevalent focused human antibody response to the influenza hemagglutinin head interface. mBio *12*(3): e0114421; 2021. doi: 10.1128/mBio.01144-21. (PMC8262862).

200. Song, S., M. Manook, J. Kwun, A.M. Jackson, S.J. Knechtle and **G. Kelsoe**. Allo-specific humoral responses: new methods for screening donor-specific antibody and characterization of

HLA-specific memory B cells. Front Immunol 2021 https://doi.org/10.3389/fimmu.2021.705140 (PMC8617053).

201. Finney, J. and **G. Kelsoe**. Continuous culture of mouse primary B lymphocytes by forced expression of *Bach2.* J Immunol 2021 Aug 13:ji2100172. doi: 10.4049/jimmunol.2100172 (PMC8313870).

202. Song, S., M. Manook, J. Kwun, A.M. Jackson, S.J. Knechtle and **G. Kelsoe**. A novel cell-based multiplex immunoassay platform. Comm Biol **4,** 1338; 2021. https://doi.org/10.1038/s42003-021-02881-w (PMC8617053).

203. Yeh, C.-H., J. Finney, T. Okada, T. Kurosaki, and **G. Kelsoe**. Germinal center resident T_{FH} are a small, physiologically distinct subset of CXCR5^{hi}PD-1^{hi} T_{FH}. Immunity **55** (2): 272-289; 2022. doi.org/10.1016/j.immuni.2021.12.015 (PMC8842852) [Reviewed in S.G. Tangye and K. Warnatz. "'Are You Gonna Go My Way?' Decisions at the Tfh B Cell Interface". Immunity **55** (3): 377-379; 2022. doi.org/10.1016/j.immuni.2022.02.002] (PMC8842852).

204. Kuraoka, M., C.H. Yeh, G. Bajic, R. Kotaki, S. Song, I. Wilson, S.C. Harrison, and **G. Kelsoe**. Recall of B cell memory depends on relative locations of prime and boost immunization. Science Immunology. Sci Immunol **7** (71); 2022. doi: 10.1126/sciimmunol.abn5311. [Journal cover; reviewed in A. Manjarrrez "Booster is best in the same limb as initial vaccine: mouse study". The Scientist (www.the-scientist.com/news-opinion/boost-in-same-limb-as-the-initial-vaccine-mouse-study-suggests-69990) and 17 additional news outlets; top 5% of all research outputs scored by Altimetric]; selected by the International Society for Vaccines (ISV) as the *ISV Paper of the Month* for August 2022 (PMC9169233).

205. Kuraoka, M., N.C. Curtis, A. Watanabe, H. Tanno, S. Shin, C. Ye, E. Macdonald, O. Lavidor, S. Kong, T.A. Von Holle, I. Windsor, G.C. Ippolito, G. Georgiou, E.B. Walter, **G. Kelsoe**, S.C. Harrison, M.A. Moody, G. Bajic, and J. Lee. Infant antibody repertoires during the first two years of influenza vaccination. mBio **13**(6):e0254622; 2023. doi: 10.1128/mbio.02546-22 (PMC9765176).

206. Haynes, B.F., K. Wiehe, P. Borrrow, K.O. Saunders, B. Korber, K. Wagh, A.J. McMichael, **G. Kelsoe**, B.H. Hahn, F. Alt, G.M. Shaw. Strategies for HIV-1 vaccines that induce broadly neutralizing antibodies. Nature Reviews Immunology **23**(3):142-158; 2023. doi: 10.1038/s41577-022-00753-w (PMC9372928). [Highly cited paper; *Essential Science Indicators*]

207. Kuraoka, M., C.B. Aschner, I.W. Windsor, A.M. Mahant, S. Garforth, S.L. Kong, J.M. Achkar, S.C. Almo, **G. Kelsoe**, and B.C. Herold. A non-neutralizing glycoprotein B monoclonal antibody protects against herpes simplex virus disease in mice. J Clin Invest **133**(3):e161968; 2023 (PMC36454639).

208. Haynes B.F., K. Wiehe, P. Borrow, K.O. Saunders, B. Korber, K. Wagh, A.J. McMichael, **G. Kelsoe**, B.H. Hahn, F.W. Alt, G.M. Shaw. Strategies for HIV-1 vaccines that induce broadly neutralizing antibodies. Nat Rev Immunol. 2023 Mar;23(3):142-158. doi: 10.1038/s41577-022-00753-w (PMID: 35962033).

209. Simmons, H.C., A. Watanabe, T.H. Oguin III, E.S. van Itallie, K.J. Wiehe, G.D. Sempowski, M. Kuraoka, **G. Kelsoe**, K.R. McCarthy. A new class of antibodies that overcomes a steric barrier to cross-group neutralization of influenza viruses.
PLoS Biol. 2023 Dec 21;21(12):e3002415. doi: 10.1371/journal.pbio.3002415.
(PMID: 38127922).

210. Finney, J., A.P. Moseman, S. Kong, A. Watanabe, S. Song, R.M. Walsh Jr., M. Kuraoka, R. Kotaki, E.A. Moseman, K.R. McCarthy, D. Liao, X. Liang, X. Nie, O. Lavidor, R. Abbott, S.C. Harrison, **G. Kelsoe**. Protective human antibodies against a conserved epitope in pre- and postfusion influenza hemagglutinin. Proc Natl Acad Sci U S A. 2024 Jan 2;121(1):e2316964120. doi: 10.1073/pnas.2316964120. (PMC10769852).

211. Simmons, H.C., J. Finney, R. Kotaki, Y. Adachi, A.P. Moseman, A. Watanabe, S. Song, L.R. Robinson-McCarthy, V. Le Sage, M. Kuraoka, E.A. Moseman, **G. Kelsoe**, Y. Takahashi, K.R. McCarthy. A protective and broadly binding antibody class engages the influenza virus hemagglutinin head at its stem interface. mBio, 2025 May 20:e0089225. (PMID: 40391889).

212. Joel Finney, J., M. Kuraoka, S. Song, A. Watanabe, X. Liang, D. Liao, M.A. Moody, E.B. Walter, S.C. Harrison, **G. Kelsoe**. Fluorescence-barcoded cell lines stably expressing membrane-anchored influenza neuraminidases. Vaccine, 2025 May 22;56:127157. (PMID: 40391889).

213. Stephanie C. Eisenbarth, F. Batista, J. Cyster, R. Elsner, **G. Kelsoe**, F. Lund, S. Pillai, I. Sanz, M. Shlomchik, K.M. Tiellner, C. Vinuesa, and N. Baumgarth. A roadmap for defining “extrafollicular” B cell responses. Immunity, 2025, *online 22 September 2025*.

OTHER PUBLISHED WORK

2. Proceedings and Reports

1. Schucany, W.R., **G. Kelsoe** and V. Allison. An efficient statistic for determining the diameter of thin sectioned spheres from measurements of biological samples. *In*: 32nd Ann. Proc. Electron Micro. Soc. Amer., St. Louis, MO. (ed., C.J. Arceneaux), p. 319-322; 1974.

2. **Kelsoe, G**., T. Takemori, M. Reth and K. Rajewsky. Generation of regulatory T cells with monoclonal anti-idiotope antibody: generation of T suppressor cells. *In*: The Proceedings of the Second International Conference of B lymphocytes in the Immune Response: functional, developmental, and interactive properties (eds. N. Klinman, D. Mosier, I. Scher, and E. Vitteta). Scottsdale, Arizona, October, 1980. Elsevier North-Holland, New York/Amsterdam, p. 423-430; 1981.

3. Eisen, H.N., K.L. Knight, M. Cooper, B.J. Fowlkes, R.H. Buckley, R.S. Geha, *et al*. Report of the NIAID Task Force on Immunology. (exec. sec., A. Nisonoff; ed., H. Quill). U.S. Department of Health and Human Services, National Institutes of Health, 217 pp., September 1998.

4. Tambur, A.R., P. Campbell, A.S. Chong, S. Feng, M.L. Ford, H. Gebel, R.G. Gill, **G. Kelsoe**, V. Kosmoliaptsis, R.B. Mannon, M. Mengel, E.F. Reed, N.M. Valenzuela, C. Wiebe, E. Dijke, H.C. Sullivan, and P. Nickerson. Sensitization in transplantation: assessment of risk (STAR) 2019 Working Group Meeting Report. Am J Transplant 20:2652-2668; 2020. doi: 10.1111/ajt.15937. (PMC7586936).

Books and Book Chapters

1. Rajewsky, K., M. Reth, T. Takemori and **G. Kelsoe**. A glimpse into the inner life of the immune system. *In*: The Immune System-a Festschrift in honor of Neils Kaj Jerne on the occasion of his seventieth birthday (eds., I. Lefkovits and C. Steinberg). S. Karger, Basel, vol. II, p. 1-11; 1981.

2. **Kelsoe, G**. Regulation of the immune response by monoclonal anti-idiotope and idiotope-bearing antibody. *In*: Idiotypes. Antigens on the Inside (ed., I. Schnurr). Hoffmann-La Roche Publishing, Basel, p. 200-211; 1982.

3. **Kelsoe, G**. (Consulting Editor), S. Baron (ed). Medical Microbiology. Addison-Wesley, Menlo Park, California; 1985.

4. **Kelsoe, G**. and D. Schulze (eds.). Evolution and Vertebrate Immunity: The antigen receptor and MHC gene families. University of Texas Press, Austin; 1987.

5. **Kelsoe, G**. and D. Farina. Is the antibody repertoire biased? *In:* Evolution and vertebrate immunity: The antigen receptor and MHC gene families (eds., G. Kelsoe and D. Schulze). University of Texas Press, Austin, p. 163-174; 1987.

6. Weido, A.J., J. Jacob, and **G. Kelsoe**. Ontogeny of the antibody repertoire. *In*: Idiotype Networks and Diseases (eds., J. Cerny and J. Hiernaux). American Society of Microbiology, Washington, D.C., p. 1-10; 1990.

7. **Kelsoe, G**. The primary antibody repertoire: the somatic genotype and paratopic phenotype of B-cell populations. *In*: Molecular Immunobiology of Self-Reactivity (eds., C.A. Bona and A.K. Kaushik). Marcel Dekker, Inc. p. 81-92; 1992.

8. Bona, C.A., **G. Kelsoe**, V. Pascual and J.D. Capra. Expression and pairing of V_H and V_L families in murine and human self-reactive antibodies. *In*: Molecular Pathology of Autoimmune Disease (eds., C.A. Bona, K. Siminovitch, M. Zanetti, and A.N. Theophilopoulos). Harwood Academic Publishers, New York, p. 65-83; 1993.
(Other published work, *continued*)

9. **Kelsoe, G**., J. Dal Porto, S. Han, C. Miller, and B. Zheng. Cellular pathways to antibody formation and immunologic memory. *In*: Handbook of Experimental Immunology (5th Edition) (eds. L.A. Herzenberg and L.A. Herzenberg). Blackwell Science Press, New York, pp. 92.1-92.8; 1997.

10. **Kelsoe, G**. and M.F. Flajnik (eds.). Somatic diversification of immune responses. Current Topics in Microbiology and Immunology, vol. 229. Springer-Verlag, Heidelberg; 1998.
(Reviewed in Exp. Clin. Immunogenet. 15: 118; 1998)

11. **Kelsoe, G**., and L.P. Hale. Architecture of the immune system [Chapter 2; pp.10-22]. *In*: Samter's Immunologic Diseases (Sixth Edition) (eds. K.F. Austen, M.M. Frank, J.P. Atkinson, and H. Cantor). Lippincott Williams & Wilkins, Philadelphia, New York; 2001.

12. Kilpatrick, M., M. Sarzotti, and **G. Kelsoe**. Induction of B cells by DNA vaccines [Chapter 4; pp. 66-81]. *In*: Medical Intelligence Unit 35. DNA Vaccines (ed. H.C.J. Ertl). Landes Bioscience, Georgetown, Texas and Kluwer Academic/Plenum Publishers, New York, New York; 2003

13. Cain, D. W. and **G. Kelsoe**. Inflammation: Acute. Encyclopedia of Life Sciences, Wiley-Blackwell, John Wiley & Sons, Ltd - The Atrium, Southern Gate - Chichester PO19 8SQ – UK; 2010.

14. Haynes, B.F., K.O. Saunders, **G. Kelsoe**, J.R. Mascola, G.J. Nabel. The cellular and molecular biology of HIV-1 broadly neutralizing antibodies [Chapter 24; pp. 441-463]. *In*: The Molecular Biology of B Cells (*second edition*) (eds., F.W. Alt, T. Honjo, A. Radbruch, and M. Reth) Academic Press/Elsevier Ltd., 32 Jamestown Road, London NW1 7BY, UK; 2015.

15. **Kelsoe, G**. and B.F. Haynes. Breaking through immunity's glass ceiling. What are the primary limitations in B cell affinity maturation? How much affinity maturation can we drive with vaccination? *In*: Immune Memory and Vaccines: Great Debates (eds. S Crotty and R. Ahmed). A Cold Spring Harbor Perspectives in Biology Collection, Cold Spring Harbor Laboratory Press, 1 Bungtown Road, Cold Spring Harbor, New York; 2018. (PMC5736460).

Public Preprint Repositories

1. Caradonna, T.M., I.W. Windsor, A.A. Roffler, S. Song, A. Watanabe, **G. Kelsoe**, M. Kuraoka, and A.G. Schmidt. An epitope-enriched immunogen increases site targeting in germinal centers. bioRXiv, https://doi.org/10.1101/2022.12.01.518697.

2. Simmons, H. C., A. Watanabe, T.H. Oguin, G.D. Sempowski, M. Kuraoka, **G. Kelsoe**, and K.R. McCarthy. A class of antibodies that overcome a steric barrier to cross-group neutralization of influenza viruses. bioRXiv, https://doi.org/10.1101/2023.04.01.535242.

3. Simmons H.C., J. Finney, R. Kotaki, Y. Adachi, A.P. Moseman, A. Watanabe, S. Song, L.R. Robinson-McCarthy, V.L. Sage, M. Kuraoka, E.A. Moseman, **G. Kelsoe**, Y. Takahashi, K.R. McCarthy. A broad antibody class engages the influenza virus hemagglutinin head at its stem interface. bioRχiv. 2023 Dec 14:2023.12.13.571543. doi: 10.1101/2023.12.13.571543. (PMID: 38168412; Preprint).

4. Simmons HC, J Finney, R Kotaki, Y Adachi, AP Moseman, A Watanabe, S Song, LR Robinson-McCarthy, V Le Sage, M Kuraoka, EA Moseman, G **Kelsoe**, Y Takahashi, KR McCarthy. A protective and broadly binding antibody class engages the influenza virus hemagglutinin head at its stem interface. bioRxiv. 2024 Jul 1:2023.12.13.571543. doi: 10.1101/2023.12.13.571543.

5. Finney J, M Kuraoka, S Song, A Watanabe, X Liang, D Liao, MA Moody, EB Walter, SC Harrison, **G Kelsoe**. Fluorescence-barcoded cell lines stably expressing membrane-anchored influenza neuraminidases. bioRxiv 2025 Jan 2:2025.01.01.631020. doi: 10.1101/2025.01.01.631020.PMID: 39803488.

Submitted/in preparation for publication

1. F. Liu, M. Kuraoka, L.G. Cowell, E. Heikamp, and **G. Kelsoe**. Evidence for spontaneous secondary *Igκ* rearrangements in small pre-B cells: implications for receptor editing, *submitted*.

2. P.B. Snowden, D.W. Cain, M. Kuraoka, T.M. Holl, M. Womble, K. Hopper, and **G. Kelsoe**. Comparable humoral responses to native and haptenated proteins in MyD-88 deficient mice, *submitted*.

3. K. Tonouchi, C.H. Yeh, D.W. Cain, E.A. Moseman, B.F. Haynes, K. Wagh, K. Wiehe, T. Kurosaki, **G. Kelsoe**. On the carrying capacity of the bone marrow survival niche in mice, Frontiers in Immunology, *in the press*.

4. S. Song, H. Li, C.H. Yeh, A. Watanabe, M. Kuraoka, H. Gao, X. Shen, C.C. LaBranche, W.B. Williams, K.O. Saunders, M.A. Moody, D.C. Montefiori, B.F. Haynes, G.M. Shaw, **G. Kelsoe**. Functional Convergence of Genetically Diverse B-Cell Receptors in Simian-HIV Infected Rhesus Macaques, *submitted*.

5. C.H. Yeh, H. Kirshner, S. Song, A. Watanabe, D. Liao, K. Wiehe, **G. Kelsoe**, M. Kuraoka. Mice deficient in BAX and BAK support normal affinity maturation and illustrate unbiased AID-driven mutation, *in preparation*.

6. J.S. Barber, K. Tonouchi, H. Kirshner, K. Wiehe, K. Saunders, M. Tian, F.W. Alt, B.F. Haynes, G. Shaw, **G. Kelsoe**. Single-cell characterization of somatic evolution to neutralization breadth in germline BCR knockin mice: asymmetrical boost responses, *in preparation*.

7. K. Tonouchi, E. van Italie, J. San, J Finney, M. Kuraoka, K. McCarthy, K. Wiehe, S.C. Harrison, **G. Kelsoe**. Antibody feedback: population genetics and dynamics of primary germinal center responses, *in preparation*.