

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner.

Case IPR2023-00442
Patent No.10,130,681 B2

EXPERT DECLARATION OF ALEXANDER M. KLIBANOV, Ph.D.

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I, Alexander Klibanov, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. (“Regeneron”) as a technical expert in connection with the above-captioned proceeding to provide my opinions and views on the issues at hand. I have reviewed the materials filed in relation to the Petition for *Inter Partes* review of U.S. Patent No. 10,130,681 (“the ’681 Patent”) (Ex. 1001). In particular, I have been asked to comment on the state of the relevant art as of the earliest filing date (“priority date”) of the ’681 Patent and to respond to the opinions and views of Petitioner’s declarant, Dr. Edward Chaum. I submit this declaration in support of Regeneron’s Patent Owner Response (“POR”).

2. I am being paid for my time spent working on this matter at my usual and customary hourly rate. I have no personal or financial stake in, or affiliation with, the petitioner, real-parties-in-interest, or the patent owner. My compensation is not dependent upon the outcome of, or my testimony in, the present proceeding.

II. QUALIFICATIONS AND EXPERIENCE

3. I am currently a Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology (“M.I.T.”), where I taught and conducted research for over 40 years. From 2014 to 2019 (and also from 2007 to 2012), I held the Novartis Endowed Chair Professorship at M.I.T. From 2012 to

2014, I held the Roger and Georges Firmenich Endowed Chair Professorship in Chemistry. Prior to that, I was a Professor of Chemistry and a Professor of Bioengineering at M.I.T., positions I held from 1988 and 2000, respectively. From 1979 to 1988, I was an Assistant Professor, then Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences (formerly the Department of Nutrition and Food Science) at M.I.T.

4. I obtained my M.S. degree in Chemistry from Moscow University in Russia in 1971 and Ph.D. in Chemical Enzymology from the same University in 1974. Thereafter, I was a Research Chemist at Moscow University's Department of Chemistry for three years. From 1977 to 1979, following my immigration to the United States, I was a Post-Doctoral Associate at the Department of Chemistry, University of California in San Diego.

5. Over the last 50 years as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of chemistry, including biological, protein, medicinal, and formulation chemistry.

6. I have earned numerous prestigious professional awards and honors. For example, I was elected to the U.S. National Academy of Sciences (considered among the highest honors that can be given to an American scientist) and also to the U.S. National Academy of Engineering (considered among the highest honors that can be given to an American engineer). I am also a Founding Fellow of the

American Institute for Medical and Biological Engineering and a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters). In addition, I have received the Arthur C. Cope Scholar Award, the Marvin J. Johnson Award, the Ipatieff Prize, and the Leo Friend Award, all from the American Chemical Society, as well as the International Enzyme Engineering Prize.

7. I currently serve on the Editorial Boards of over a dozen scientific journals, including "Open Journal of Pharmacology", "Applied Biochemistry and Biotechnology", "Nanocarriers", "Open Access Academic Books in Chemistry", "Biotechnology and Bioengineering", "Journal of Biological Chemistry and Molecular Pharmacology", "Recent Patents in Biotechnology", "Archives of Medical Biotechnology", "Current Pharmaceutical Biotechnology", and "International Journal of Drug Design, Delivery, and Safety."

8. I have published over 315 scientific papers in various areas of chemistry. Of particular relevance to this proceeding are my numerous publications specifically dealing with protein chemistry, therapeutic proteins, and treatment of ophthalmological disorders (*i.e.*, diseases of the eye). I am also a named inventor of 32 issued United States patents and of a number of pending ones. I have given over 370 invited lectures, including many distinguished named lectureships, at professional conferences, universities, and corporations all over the world, many dealing with formulation, stability, stabilization, and biological evaluation of

pharmaceutically active proteins (including enzymes and their inhibitors, as well as antibodies and growth factors). According to a recent Stanford University-led study, the overall impact of my published work places me in the top 0.01% of all scientists in the world.

9. In addition to my research and teaching activities at M.I.T., I have consulted widely for pharmaceutical, medical device, and biotechnology companies. Those consulting relationships have included both innovator and generic pharmaceutical companies.

10. I also have founded six pharmaceutical companies and have been on the scientific advisory boards and/or boards of directors of those companies and of many others. Of particular relevance to the present proceeding, one of the pharmaceutical companies founded by me focused on intravenous and subcutaneous delivery of therapeutic antibodies and fusion proteins.

11. A number of the aforementioned consulting, advisory, and directorship activities have dealt specifically with formulation (such as liquid), stabilization, administration (including parenteral), posttranslational modification, testing, and medical applications of therapeutically active proteins.

12. My *curriculum vitae*, attached as Ex. 2061, summarizes my education and academic experience. Included in it is a list of all my professional publications and patents.

III. SUMMARY OF OPINIONS

13. My opinions and views set forth in this declaration are based on my education, training, and experience, as well as the materials I reviewed in preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '681 Patent at the time of its earliest priority date.

14. In forming my opinions, I have reviewed the following materials: (a) the Petition for *Inter Partes* Review of the '681 Patent, IPR2023-00442 (Paper 2), including all cited exhibits; (b) all other documents and references cited throughout this declaration; and (c) Patent Owner's Response to which my declaration relates.

15. It is my opinion that the references identified by Dr. Chaum—Dixon (Ex. 1006), CATT (Ex. 1031), MACTEL (Ex. 1032-33), and PIER (Ex. 1034)—do not disclose either the amino acid sequence or the nucleic acid sequence of VEGF Trap-Eye.

16. It is also my opinion that the prior art did not disclose that VEGF Trap-Eye necessarily had the same amino acid sequence as aflibercept.

IV. A PERSON OF ORDINARY SKILL IN THE ART

17. I am informed that a person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to have access to, and be aware of, all of the relevant publicly available prior art at the time of the invention.

18. In forming my opinions expressed herein, I have been asked to consider the level of ordinary skill in the art as it relates to the '681 Patent as of its effective filing date. I understand that the application that led to the '681 Patent was filed on March 28, 2017. I further understand that the '681 Patent claims priority to provisional applications filed on January 13, 2011, January 21, 2011, and November 21, 2011. I have been informed that the earliest filing date of the '681 Patent is January 13, 2011.

19. Petitioner contends that the definition of a POSA adopted in the Final Written Decision in IPR2021-00881 (Ex. 1004) also should be applied with respect to the '681 Patent, such that a POSA would have:

(1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

See Paper 2 (Petition) at 17-18. Petitioner further contends that “a POSA would not necessarily be an ophthalmologist, but would have similar knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration

of therapies to treat said disorders.” *Id.* at 18-19.

20. I understand that Patent Owner contends that a POSA is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists.

21. My opinions set forth in this declaration remain the same under either Petitioner’s or Patent Owner’s definition of a POSA.

V. LEGAL STANDARDS

22. I am not an attorney or an expert in U.S. patent law. The following legal standards I have applied in forming my opinions expressed in this declaration were explained to me by counsel for Patent Owner (“counsel”).

A. Burden of Proof

23. Each claim of an issued patent is presumed to be valid. To overcome that presumption of validity, the party challenging the claim’s validity must establish unpatentability by a preponderance of the evidence (*i.e.*, more likely than not).

B. Obviousness

24. For a patent to be valid, the claimed invention must be non-obvious to a POSA at the time of the claimed invention.

25. A patent claim is obvious in view of the prior art if the differences between the patented claim and the prior art are such that, at the time of the invention, the claimed subject matter as a whole would have been obvious to a POSA.

26. A prior art reference may inherently disclose a claim limitation if the limitation is necessarily present or is the natural result of expressly disclosed prior art elements. But inherency cannot be established by probabilities or possibilities—the mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. Inherency may not be relied upon to supply the identity of a prior art product that was not known or determinable based on the prior art disclosures of its characteristics.

27. Obviousness cannot be predicated on what was unknown to a POSA at the time an invention was made. Thus, inherency may not be relied upon to supply a missing claim limitation in the obviousness context unless the missing limitation is both inherent and expected. The path that led an inventor to the claimed invention is irrelevant to the obviousness analysis.

28. Accordingly, in the case of the '681 Patent, a POSA would have to have known, by January 13, 2011, that the disclosure of “VEGF Trap-Eye” in Petitioner’s references necessarily corresponds to the recited amino acid sequence or the recited nucleic acid sequence of the challenged claims, or that at least one of these recited sequences is a natural result of the combinations of elements explicitly disclosed by the prior art, in order for Petitioner to be able to prove inherent obviousness of that claim limitation in view of the cited prior art references.

VI. The '681 Patent

29. The '681 Patent is titled "Use of a VEGF [where VEGF stands for the protein Vascular Endothelial Growth Factor] Antagonist to Treat Angiogenic Eye Disorders." I understand that Petitioner has challenged claims 1, 3-11, 13-14, 16-24, and 26 of the '681 Patent ("the Challenged Claims").

30. The '681 Patent has two independent claims, 1 and 14. Claim 1, reproduced below, is representative:

A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Ex. 1001 at 21:40-63.

31. A POSA would understand that claim 1 is directed to the treatment of an angiogenic eye disorder with a VEGF (a signaling protein that stimulates the formation of blood vessels) antagonist that has the amino acid sequence of SEQ ID NO:2.

32. Claim 14 differs from claim 1 with respect to the last “wherein” clause, which recites the nucleic acid sequence of SEQ ID NO:1, corresponding to the amino acid sequence of SEQ ID NO:2. Ex. 1001 at 23:5-23.

33. Dependent claims 3-11, 13, 16-24, and 26 of the '681 Patent further limit the time between dose administrations, the specific angiogenic eye disorder, administration route, and dose amount.

VII. EYLEA[®]

34. Eylea[®] is a marketed drug containing vascular endothelial growth factor (VEGF) antagonist as the active pharmaceutical ingredient (“API”) that is indicated, among other things, for “the treatment of patients with: Neovascular (Wet) Age-Related Macular Degeneration (AMD).” Ex. 2063¹ at 1 (INDICATIONS AND

¹ Eylea[®] Prescribing Information (rev. 05/2019).

USAGE). Eylea[®] was approved by the FDA for the treatment of wet AMD (“wAMD”) on November 18, 2011. *See* Ex. 2064 at 1.²

35. The API in Eylea[®] is the recombinant fusion protein aflibercept, which consists of “portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1.” Ex. 2063 (Eylea[®] Prescribing Information) at section 11.

36. Eylea[®] is “formulated as an iso-osmotic solution for intravitreal administration [*i.e.*, injection into the eye].” Ex. 2063 (Eylea[®] Prescribing Information) at section 11.

VIII. NEITHER THE AMINO ACID SEQUENCE NOR THE NUCLEIC ACID SEQUENCE OF VEGF TRAP-EYE IS NECESSARILY PRESENT IN THE PRIOR ART REFERENCES RELIED ON BY DR. CHAUM

A. Dixon (Ex. 1006)³

37. Dixon (Ex. 1006) is titled “VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration.” Dixon was published in 2009 in the journal *Expert Opinion on Investigational Drugs*. Dixon states that “[s]tructurally, VEGF Trap-Eye is” “a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.” Ex. 1006 at 1575-76.

² Eylea[®] Approval Letter (November 18, 2011).

³ Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18 *EXPERT OPINION ON INVESTIGATIONAL DRUGS* 1573 (2009) (“Dixon”).

Dixon also reports that “VEGF Trap-Eye and [Regeneron’s] aflibercept (the oncology product) have the same molecular structure, but there are *substantial differences* between the preparation of the purified drug product and their formulations.” *Id.* at 1575 (emphasis added). In the same paragraph, Dixon subsequently states that “VEGF Trap-Eye undergoes further purification steps during manufacturing” and “is also formulated with different buffers and at different concentrations (for buffers in common)” compared to the oncology product aflibercept. *Id.*

38. Dixon does *not* disclose (i) the amino acid sequence or the nucleic acid sequence of either VEGF Trap-Eye or aflibercept; (ii) which particular amino acid residues of the VEGF receptor-1 or receptor-2 domains are included in VEGF Trap-Eye; (iii) which particular amino acid residues of the Fc domain (the crystallizable, *i.e.*, the tail, region of an antibody) form “the Fc fragment” of VEGF Trap-Eye; and/or (iv) that VEGF Trap-Eye has the same amino acid sequence as aflibercept.

B. CATT (Ex. 1031)⁴, MACTEL (Exs. 1032⁵-1033⁶), and PIER (Ex. 1034)⁷

39. CATT (Ex. 1031) is a document titled “CATT PATIENT ELIGIBILITY CRITERIA.” MACTEL (Exs. 1032-1033) provide historical changes for the MACTEL 2 clinical trial and an archived description. PIER (Ex. 1034) is a journal article titled “Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1.” The PIER article was published in 2008 in the American Journal of Ophthalmology and reports the results of the first year of the PIER clinical study. None of CATT, MACTEL, and PIER provides any information regarding the amino acid sequence or the nucleic acid sequence of either VEGF Trap or VEGF Trap-Eye, much less that VEGF Trap-Eye has the same amino acid sequence as aflibercept. I

⁴ CATT Patient Eligibility Criteria (July 13, 2010), available at: https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf (“CATT”).

⁵ Ranibizumab Injections to Treat Macular Telangiectasia without New Blood Vessel Growth (NCT00685854) (May 24, 2008), available at: https://clinicaltrials.gov/ct2/history/NCT00685854?V_1=View#StudyPageTop (“MACTEL Study”).

⁶ Ranibizumab Injections to Treat Macular Telangiectasia without New Blood Vessel Growth (NCT00685854) (November 7, 2008), available at: <https://web.archive.org/web/20081107014243/https://clinicaltrials.gov/ct2/show/NCT00685854> (“MACTEL Study Wayback Machine”).

⁷ Regillo et al., *Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1*. 145 AM. J. OPHTHALMOL. 239 (2008) (“PIER”).

further understand that Petitioner does not rely on any of CATT, MACTEL, and/or PIER for its arguments relating to the sequence limitations of the Challenged Claims.

IX. NEITHER THE AMINO ACID SEQUENCE NOR THE NUCLEIC ACID SEQUENCE OF VEGF TRAP-EYE IS NECESSARILY PRESENT IN THE ADDITIONAL VEGF TRAP REFERENCES IDENTIFIED BY DR. CHAUM

A. Holash (Ex. 1009)⁸

40. Holash (Ex. 1009) is titled “VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects.” It was published in 2002 in the journal the Proceedings of the National Academy of Sciences of the U.S.A.

41. Holash does *not* disclose (i) the amino acid sequence or the nucleic acid sequence of either VEGF Trap-Eye or aflibercept; (ii) which particular amino acid residues of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2 are included in VEGF-Trap_{R1R2}; (iii) which particular amino acid residues of the Fc domain (the crystallizable, *i.e.*, the tail, region of an antibody) form “the constant region (Fc) of human IgG1” of VEGF-Trap_{R1R2}; and/or (iv) that VEGF Trap-Eye either is the same as VEGF-Trap_{R1R2} or has the same amino acid sequence as aflibercept.

⁸ Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PROC. NAT’L ACAD. SCIS. USA 11393 (2002) (“Holash”).

B. Gomez-Manzano (Ex. 1011)⁹

42. Gomez-Manzano (Ex. 1011) is a 2008 journal article titled “VEGF Trap Induces Antiglioma Effect at Different Stages of Disease.”

43. Gomez-Manzano does **not** disclose (i) the amino acid sequence or the nucleic acid sequence of either VEGF Trap-Eye or aflibercept (or VEGF Trap for that matter); (ii) which particular domains of VEGFR1 and VEGFR2 are included in VEGF Trap; (iii) which particular amino acid residues of the selected domains of VEGFR1 and VEGFR2 are included in VEGF Trap; (iv) which particular amino acid residues of the Fc domain (the crystallizable, *i.e.*, the tail, region of an antibody) form “the constant region of human immunoglobulin G1” of VEGF Trap; and/or (v) that VEGF Trap-Eye either is the same as VEGF Trap or has the same amino acid sequence as aflibercept.

C. Adis R&D Profile (Ex. 1012)¹⁰

44. Adis R&D Profile (Ex. 1012) is titled “Aflibercept” and lists a number of other names in the subtitle—AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), and VEGF Trap-Eye. Ex. 1012 at 1. The Adis paper was published in the journal Drug in R&D in 2008. It is anonymous, *i.e.*,

⁹ Gomez-Manzano et al., *VEGF Trap Induces Antiglioma Effect at Different Stages of Disease*, 10 NEURO-ONCOLOGY 940 (2008) (“Gomez-Manzano”).

¹⁰ Adis R&D Profile, *Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye*, 9 DRUGS in R&D 261 (2008) (“Adis”).

conspicuously provides no information as to who its authors are and/or their affiliations, which is contrary to generally-accepted scientific publishing norms. Adis provides no amino acid or nucleic acid sequence information for aflibercept, VEGF Trap-Eye, or any other Trap product candidate. Nor does Adis state that the term “VEGF Trap-Eye” corresponds to only aflibercept. Rather, Adis states that “[a]flibercept is a member of Regeneron’s proprietary family of ‘Trap’ product candidates....” *Id.* Furthermore, some of the names that Adis lists in its subtitle next to aflibercept, *e.g.*, VEGF Trap - Regeneron and VEGF Trap (R1R2), were known in the art to encompass a genus of fusion proteins. *See* Ex. 1009¹¹ at 11393-94 and paragraph 81 below.

45. In addition, Adis reads as a piece of commercial intelligence in the pharmaceutical industry rather than a scientific article. According to the Drugs in R&D website, the journal was re-launched in 2010 and has been since peer-reviewed. However, I have seen no evidence that it had been also peer-reviewed in 2008 when Adis was published, especially since it is clearly not a regular scientific article. Due to all of the foregoing, it is my opinion that a POSA would not view Adis as a source of accurate and/or reliable protein chemistry information. Nor would a POSA consider the information in Adis to be representative of the prior art

¹¹ Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PROC. NAT’L ACAD. SCIS. USA 11393 (2002) (“Holash”).

as a whole. In particular, Regeneron's clinical trial submissions (Exs. 2358¹² & 2356¹³), press releases (Exs. 1007¹⁴ & 2361¹⁵), and filings with the SEC (Ex. 1057¹⁶ at 18-20) consistently use the term VEGF Trap-Eye for Regeneron's ophthalmology product and the term aflibercept for its oncology product. Moreover, Adis's description of the trial design of the VIEW 1/2 clinical studies (at 3) appears to be inconsistent with the descriptions provided in Regeneron's clinical trial submissions (Ex. 2358 at 6-9; Ex. 2356 at 5-6) and press releases (Ex. 1007 at 1; 2361 at 1), or even with Dixon (Ex. 1006 at 1576). *See also* Ex. 2362¹⁷ at 4-5 ("Two identical,

¹² *Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1)*, NCT00509795, CLINICALTRIALS.GOV (Apr. 28, 2009), <https://clinicaltrials.gov/ct2/show/NCT00509795> ("NCT-795").

¹³ *VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)*, NCT00637377, CLINICALTRIALS.GOV (Mar. 17, 2008), <https://clinicaltrials.gov/ct2/show/NCT00637377> ("NCT-377").

¹⁴ Press Release, Regeneron, Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (Sept. 14, 2009), <https://newsroom.regeneron.com/node/10806/pdf> ("Regeneron (14-September-2009)").

¹⁵ Press Release, Regeneron Pharms., Inc., *Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration* (May 8, 2008), <http://investor.regeneron.com/releasedetail.cfm?ReleaseID=394065> ("Regeneron (8-May-2008)").

¹⁶ REGENERON PHARMS., INC., QUARTERLY REPORT (FORM 10-Q) (Sept. 30, 2009) ("2009 10-Q").

¹⁷ Heier, *VEGF Trap-Eye for Exudative AMD*, RETINAL PHYSICIAN (Apr. 1, 2009) ("Heier Retinal Physician 2009").

noninferiority Phase 3 studies called VIEW 1 and VIEW 2 ... are currently under way to examine the effects of VEGF Trap-Eye in wet AMD.”). A POSA would consider Regeneron’s repeated statements to government agencies and to the public to be more authoritative than the generic statements made in Adis that cannot be attributed to any specific source. As such, and in context, a POSA would not consider the statements in Adis concerning aflibercept to establish that aflibercept and VEGF Trap-Eye are the same protein molecule. *See* Ex. 1002 at ¶ 51. Instead, a POSA would understand that the prior art as a whole did **not** disclose that VEGF Trap-Eye necessarily had the same amino acid sequence as aflibercept.

D. Rudge 2007 (Ex. 1014)¹⁸

46. Rudge 2007 (Ex. 1014) is a journal article titled “VEGF Trap Complex Formation Measures Production Rates of VEGF, Providing a Biomarker for Predicting Efficacious Angiogenic Blockade.”

47. Rudge 2007 does **not** disclose (i) the amino acid sequence or the nucleic acid sequence of either VEGF Trap-Eye or aflibercept (or VEGF Trap for that matter); (ii) which particular amino acid residues of the second Ig domain of human VEGFR1 and the third Ig domain of human VEGFR2 are included in VEGF Trap; (iv) which particular amino acid residues of the Fc domain (the crystallizable, *i.e.*,

¹⁸ Rudge et al., *VEGF Trap Complex Formation Measures Production Rates of VEGF, Providing a Biomarker for Predicting Efficacious Angiogenic Blockade*, 104 PROC. NAT’L ACAD. SCIS. USA 18363 (2007). (“Rudge 2007”)

the tail, region of an antibody) form “the constant region (Fc) of human Ig IgG1” of VEGF Trap; and/or (v) that VEGF Trap-Eye either is the same as VEGF Trap or has the same amino acid sequence as aflibercept.

X. THE CHALLENGED CLAIMS ARE NOT OBVIOUS

A. The Prior Art Did Not Disclose That VEGF Trap-Eye Necessarily Has the Same Amino Acid Sequence as Aflibercept

48. While today it is recognized that VEGF Trap-Eye has the same amino acid sequence as aflibercept, in 2011 this fact was *not* known from any publicly available prior-art disclosures, including the prior art identified by Petitioner and its declarant Dr. Chaum.

1. A POSA would not understand Dixon’s phrase “molecular structure” to necessarily correspond to the amino acid sequence

49. Dr. Chaum opines that Dixon’s statement that VEGF Trap-Eye and aflibercept “have the same molecular structure” (Ex. 1006 at 1575) somehow establishes that their amino acid sequences are the same. Ex. 1002 at ¶¶ 50-51, 96, 122-129.

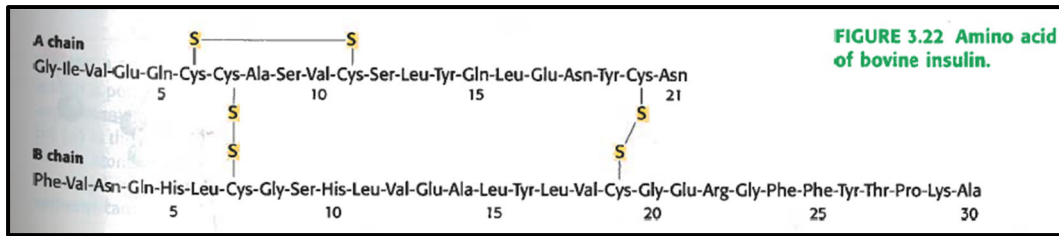
50. In its Institution Decision in this proceeding, the PTO Board concluded that there was a “reasonable likelihood” that the challenged claims of the ’681 Patent were anticipated by Dixon, incorporating the same rationale as previously set forth in the Final Written Decision in IPR2021-00881 (“the ’881 Decision”; Ex. 1004). Paper 10 at 15 (citing the ’881 Decision at 26-46). For the reasons that follow, I

disagree with Dr. Chaum's opinion and the Board's conclusion with regard to this particular issue.

51. It is well established that protein molecules, like VEGF Trap-Eye, have multiple levels of "structure," including primary, secondary, tertiary, and quaternary structures. Ex. 2065¹⁹ at 4; *see also* IPR2021-00881, Paper 94 ("the '881 Decision"; Ex. 1004) at 32-33; IPR2021-00880, Paper 89 ("the '880 Decision"; Ex. 1046) at 50-51.

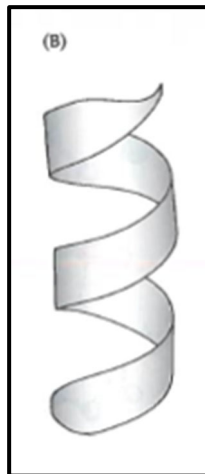
52. Proteins are formed by covalently linking the α -carboxyl group of one of the 20 standard amino acids to the α -amino group of another by means of a peptide bond. Ex. 2065 at 9. A series of amino acids joined by peptide bonds form a linear polypeptide chain. *Id.* The primary structure of a protein refers to the sequential order in which the amino acids (referred to as amino acid residues when within a polypeptide) are arranged in a polypeptide chain—*i.e.*, the amino acid sequence. *Id.* at 10. Each protein "has a unique, precisely defined amino acid sequence." *Id.* For example, an amino acid sequence for the protein bovine insulin is shown below (where each three-letter abbreviation corresponds to a particular one of the 20 standard amino acid residues):

¹⁹ Excerpts from the textbook by Jeremy M. Berg et al., BIOCHEMISTRY (5th Edn., Freeman, New York, 2002).



Id. at Fig. 3.22.

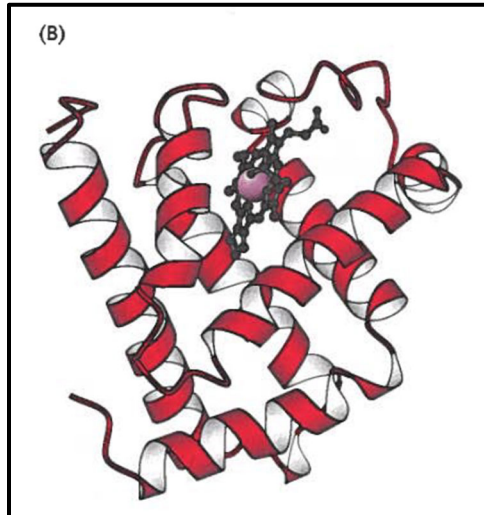
53. Polypeptide chains can spontaneously fold into localized, regular three-dimensional structures, such as α -helices or β -sheets. Ex. 2065 at 12-13. The distribution of such structures as α -helices or β -sheets along a protein chain is often referred to as its “secondary structure.” Ex. 2065 at 12. A pictorial depiction of an α -helix is reproduced below as an example:



Id. at 13, Fig. 3.32(B).

54. The overall three-dimensional structure of a protein is referred to as its “tertiary structure.” Ex. 2065 at 14-15. Typical proteins under physiological conditions fold into compact, roughly globular structures with non-polar cores. A

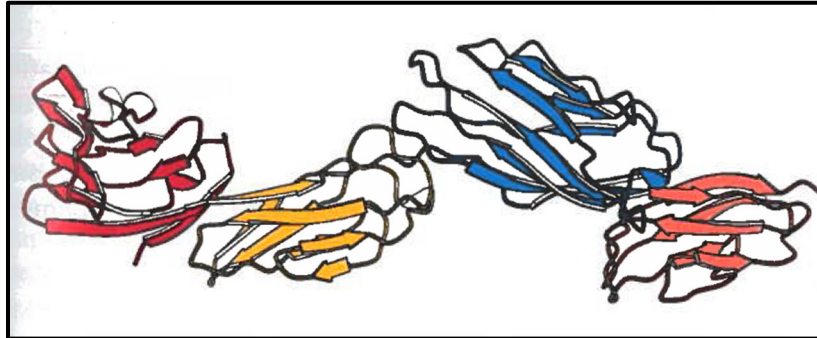
pictorial depiction of the muscle protein myoglobin (with its bound heme moiety) is shown below:



Ex. 2065 at 14, Fig. 3.44(B).

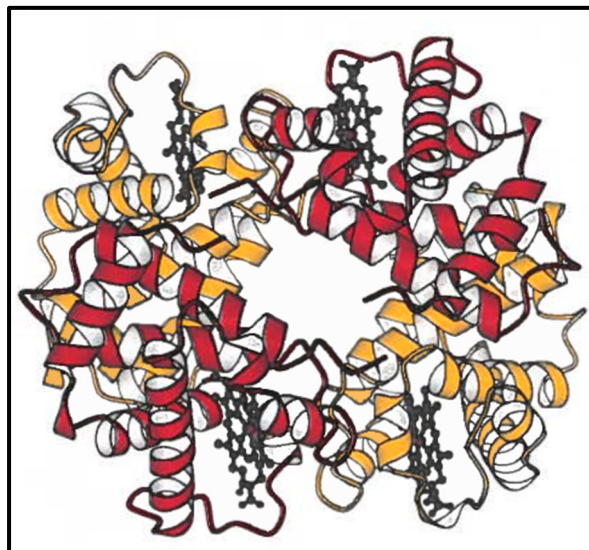
55. The tertiary structure of many proteins consists of two or more distinct, compact, and nearly mutually independent regions called “domains” connected by flexible polypeptide segments. Ex. 2065 at 15. Generally, each domain can fold and function almost independently from the rest of the protein molecule and form a self-stabilizing domain structure. These domains typically range in size from about 30 to about 400 amino acid residues. *Id.* Some proteins have certain domains in

common even if their overall tertiary structures are different. Ex. 2065 at 15. A pictorial representation of a protein with four domains is shown below:



Id. at Fig. 3.47.

56. Proteins comprising more than one polypeptide chain exhibit a level of three-dimensional structure referred to as their “quaternary structure.” Each such polypeptide chain is called a “subunit,” and the quaternary structure “refers to the spatial arrangement of subunits and the nature of their interactions.” Ex. 2065 at 16. For example, human hemoglobin consists of four subunits as shown below:



Id. at Fig. 3.49.

57. While Dr. Chaum acknowledges that proteins “have primary, secondary, tertiary, and quaternary structure,” he fails to even mention, let alone account for, a protein’s domain structure in his declaration. *See, e.g.*, Ex. 1002 at ¶¶ 125-127.

58. I have reviewed the “VEGF Trap-Eye Sequence” section of the ’881 Decision (Ex. 1004). I understand that, based on an excerpt from William H. Brown et al., *Polypeptides and Proteins*, Chapter 27.3, in *ORGANIC CHEMISTRY* 1075-96 (4th Edn.) (2005) (“Brown textbook,” Ex. 3002 in IPR2021-00881),²⁰ the PTO Board concluded that “primary, secondary, and tertiary structures are all interrelated, and primary structure necessarily drives secondary and tertiary structures.” The ’881 Decision (Ex. 1004) at 33. I also note that the Board made similar conclusions in the ’880 Decision (Ex. 1046) at 50-51. I disagree with the Board’s conclusion that the “primary structure necessarily drives” the final three-dimensional shape of the protein, including its overall “tertiary structure[.]” The ’881 Decision (Ex. 1004) at 33; *see also* the ’880 Decision (Ex. 1046) at 51.

59. Having reviewed the Board’s cited excerpt from the Brown textbook in Ex. 3002, I find nothing in it that contradicts my previously offered opinions. For example, the Brown textbook’s discussion of primary, secondary, tertiary, and

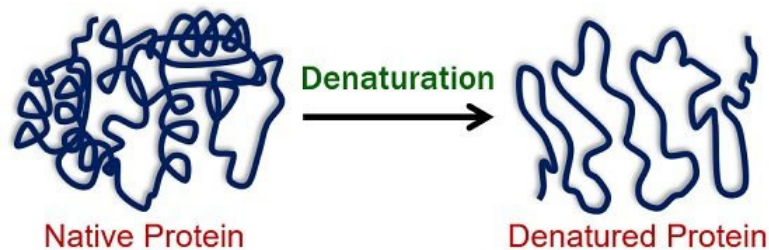
²⁰ A complete copy of Chapter 27 from William H. Brown et al., in *ORGANIC CHEMISTRY* (4th Edn., 2005) is provided as Ex. 2066.

quaternary structures is consistent with my prior testimony and declaration (Ex. 2049 in IPR2021-00880 and Ex. 2049 in IPR2021-00881 at ¶¶ 50-65), and in paragraphs 51-56 above and paragraphs 62, 65, 67-72, and 76-77 below.

60. I do not, however, find any statement in the Brown textbook that supports the Board's conclusion that the "primary structure *necessarily* drives" or unambiguously "*defin[es]* the final three-dimensional shape of the protein." The '881 Decision (Ex. 1004) at 32-33; the '880 Decision (Ex. 1046) at 50-51 (emphases added). I also note that Petitioner cites to the Brown textbook (Ex. 1038, 1095) for stating that the primary structure "necessarily drives the secondary and tertiary structures" (Paper 2 at 36), but Brown does not include, and does not support, that statement. The Brown textbook actually shows *the opposite*, as discussed below.

61. For example, the Brown textbook discusses the well-known phenomenon of denaturation of proteins in chapter 27, the same chapter cited by the Board. The Brown textbook correctly notes that protein denaturation "stems from changes in secondary, tertiary, and quaternary structure through disruption of noncovalent interactions including hydrogen bonding and hydrophobic interactions." Ex. 2066 (Brown textbook) at 55. Indeed, a POSA would know that the noncovalent interactions in a protein can be disrupted by many environmental factors, such as changes in pH, denaturants like concentrated urea and guanidine hydrochloride aqueous solutions, organic solvents, and heat. These environmental factors may

cause a protein to change its three-dimensional structure, including “secondary and tertiary structures.” A pictorial schematic representation of protein denaturation is as follows:



As illustrated above, a POSA would recognize that a protein’s three-dimensional structure can be changed, and often drastically so, even though the underlying primary structure (*i.e.*, the amino acid sequence) remains exactly the same. A POSA would also recognize that a native protein’s three-dimensional structure may be partially altered or denatured to various degrees without any changes to the underlying primary structure. Thus, a protein with the same primary structure can exist in multiple distinct secondary and/or tertiary structures. This is just one instructive example of how the primary structure ***does not necessarily*** drive or define the secondary or tertiary structures of a protein, in addition to the numerous examples presented in my prior declarations (Ex. 2049 in IPR2021-00880 and Ex. 2049 in IPR2021-00881 at ¶¶ 58-63) and below at paragraphs 67-72.

62. Based on the teachings in the prior art, a POSA would understand that Dixon’s statements concerning the “molecular structure” of VEGF Trap-Eye could refer to its quaternary, tertiary, domain, secondary, or primary structures, rather than

necessarily to its primary structure (*i.e.*, the amino acid sequence). From my review of the Board’s Final Written Decision in the ’881 proceeding, it appears the Board misunderstood my testimony to be that the phrase “molecular structure” in Dixon refers “*only* to the three-dimensional secondary and tertiary structures” of VEGF Trap-Eye and of the fusion protein and “*exclude[s]* [the possibility that the phrase refers to] the primary structure.” The ’881 Decision (Ex. 1004) at 32, 34 (emphases added); *see also* the ’880 Decision (Ex. 1046) at 49, 52. To the extent that this is the Board’s understanding, it misinterprets my testimony.

63. Contrary to the Board’s suggestion, I did not testify that “the primary structure of protein should be *omitted* from the definition of ‘molecular structure.’” The ’881 Decision (Ex. 1004) at 34 (emphasis added); *see also* the ’880 Decision (Ex. 1046) at 52.

64. Rather, my view has been, and continues to be, that the term “molecular structure” is not limited *only* to the primary, or secondary, or domain, or tertiary, or quaternary structure of a protein. In other words, while the term could be understood and/or used by a POSA to refer to a protein’s primary structure, it *also* could refer to other protein structure levels, such as the secondary, or domain, or tertiary, or quaternary structure. And stating that one of these higher levels of structure is “the same” between two protein molecules does not *necessarily* mean that those molecules also have identical primary structures. *See, e.g.*, paragraphs 67-76 below.

Therefore, the term “molecular structure” does not *necessarily* refer to a protein’s amino acid sequence. Said another way, the assertion in Dixon that VEGF Trap Eye and aflibercept have “the same molecular structure” could mean to a POSA that the proteins have the same secondary, tertiary, domain, quaternary, *or* primary structure, *not* that VEGF Trap Eye and aflibercept *necessarily* have the same secondary, tertiary, domain, quaternary, *and* primary structure. In fact, as detailed more fully below, when read in the context of the Dixon reference as a whole, the phrase “the same molecular structure” is most reasonably interpreted as meaning to a POSA that the two proteins share *the same domain structure*.

65. Indeed, as of the priority date, the term “molecular structure” was often used in the protein literature to refer to the three-dimensional structure of the protein molecule, rather than to its amino acid sequence. *See, e.g.,* Ex. 2067²¹ at 1449 (using the term “molecular structure” on no fewer than three separate occasions within the cited single first page and invariably doing so in referring to the protein’s three-dimensional, including domain, structures, such as: “This study was designed to disclose the *molecular structure* of tau [proteins] ... and has allowed us to reveal for the first time that tau is a rodlike [three-dimensional] structure”) (emphasis

²¹ Hirokawa et al., *Tau Proteins: The Molecular Structure and Mode of Binding on Microtubules*, 107 J. CELL BIOL. 1449 (1988).

added); *see also* Ex. 2068²² at 61 (observing that the binding of the gas xenon (Xe) to the muscle protein myoglobin results in “very little perturbation of the surrounding **molecular structure**.”) (emphasis added); Ex. 2069²³ at 3773 (discussing the protein hemoglobin adopting two “molecular structures” or conformations, further discussed below in paragraphs 73-74); Ex. 2070²⁴ at 10270 (“The **molecular structure** consists of β sheet regions ... interleaved with predominantly 3₁-helical parts”) (emphasis added); Ex. 2071²⁵ at 711 (stating that “[i]n the 1990s the **molecular structure** of the collagen protein was determined”) (emphasis added); Ex. 2071 (Handgraaf) at 713 Fig. 1 (providing a figure illustrating the “[**m**]olecular structure of the collagen-like [Ac-(Gly-Pro-Hyp)₆-NH₂]₃ triple helix peptide.”) (emphasis added); Ex. 2072²⁶ at 1430 (“The objectives of this novel study were to investigate the relationship between protein

²² Prangé et al., *Exploring Hydrophobic Sites in Proteins with Xenon or Krypton*, 30 PROTEINS: STRUCTURE, FUNCTION, & GENETICS 61 (1998). *See also* reference no. 33 in this publication.

²³ Mihailescu et al., *A Signature of the T $\rightarrow$ R Transition in Human Hemoglobin*, 98 PROC. NAT’L ACAD. SCIS. USA 3773 (2001) (“Mihailescu”).

²⁴ Beek et al., *The Molecular Structure of Spider Dragline Silk: Folding and Orientation of the Protein Backbone*, 99 PROC. NAT’L ACAD. SCIS. USA 10266 (2002).

²⁵ Handgraaf et al., *Molecular Dynamics Study of Onset of Water Gelation Around the Collagen Triple Helix*, 64 PROTEINS 711 (2006) (“Handgraaf”).

²⁶ Yu et al., *Relationship of Protein Molecular Structure to Metabolisable Proteins in Different Types of Dried Distillers Grains with Solubles: A Novel Approach*, 104 BRIT. J. NUTRITION 1429 (2010).

molecular structures (in terms of protein α -helix and β -sheet intensity and their ratio ...).”) (emphasis added).

66. In fact, it was well recognized in the pre-2011 art that different amino acid sequences can fold into the same three-dimensional protein structure. For example, researchers studying protein folding—the process by which a linear polypeptide chain attains its ultimate three-dimensional structure—recognized “[t]he study of proteins with the same architecture, but different [amino acid] sequence” “to be a valuable tool.” Ex. 2073²⁷ at 195. Specifically, it was known that “[t]he comparison of folding pathways in *proteins with the same structure but different sequence* is thus one way to reduce the complexity of the [protein] folding problem.” *Id.* (emphasis added).

67. Notably, over 1000 pairs of proteins with similar molecular structures but *dissimilar* amino acid sequences were available in the distant aligned protein structures (“DAPS”) database. Ex. 2074 at 1019, 1026.²⁸

68. For example, “oxidized bovine and murine C_H3 [antibodies domains] have *surprisingly similar structures* and stabilities, *considering the marginal*

²⁷ Scott et al., *The Folding of Spectrin Domains I: Wild-type Domains Have the Same Stability but Very Different Kinetic Properties*, 344 J. MOL. BIOL. 195 (2004).

²⁸ Kleiger et al., *The 1.7 Å Crystal Structure of BPI: A Study of How Two Dissimilar Amino Acid Sequences Can Adopt the Same Fold*, 299 J. MOL. BIOL. 1019 (2000) (“Kleiger”).

sequence conservation between the two molecules.” Ex. 2075²⁹ at 41 (emphases added); *see also id.* at 43 (“Surprisingly, the bC_{H3} and mC_{H3} [circular dichroism (CD)] spectra were nearly superimposable, indicating that their [*i.e.*, C_{H3}] structures must be nearly identical. This was unexpected considering bC_{H3} and mC_{H3} are only 54% identical in sequence.”).

69. Likewise, researchers investigating the crystal structure of human bactericidal/permeability-increasing protein (BPI) noted that “many proteins with no apparent sequence similarity display the same folds” and “dissimilar protein [*i.e.*, amino acid] sequences [can] adopt similar folds.” Ex. 2074 (Kleiger) at 1019. They found that “BPI has two domains with the same fold”—“twisted, anti-parallel β -sheet barrels capped by two α -helices”—but have “dissimilar sequences.” *Id.* Specifically, they identified that “two dissimilar amino acid sequences can adopt ***the same [protein] fold***,” referring to the three-dimensional structure of the protein. *Id.* (emphasis added).

70. The prior art also taught that proteins could have the same tertiary structure and retain functionality while having different primary structures—*i.e.*, different amino acid sequences. For example, thioesterases, an enzymic protein family whose members hydrolyze thioester bonds, can have “***very different primary***

²⁹ Demarest et al., *Optimization of the Antibody C_{H3} Domain by Residue Frequency Analysis of IgG Sequences*, 335 J. MOL. BIOL. 41 (2004).

structures but *common tertiary structures* and [catalytic] mechanisms.” Ex. 2076³⁰ at 1292 (emphases added).

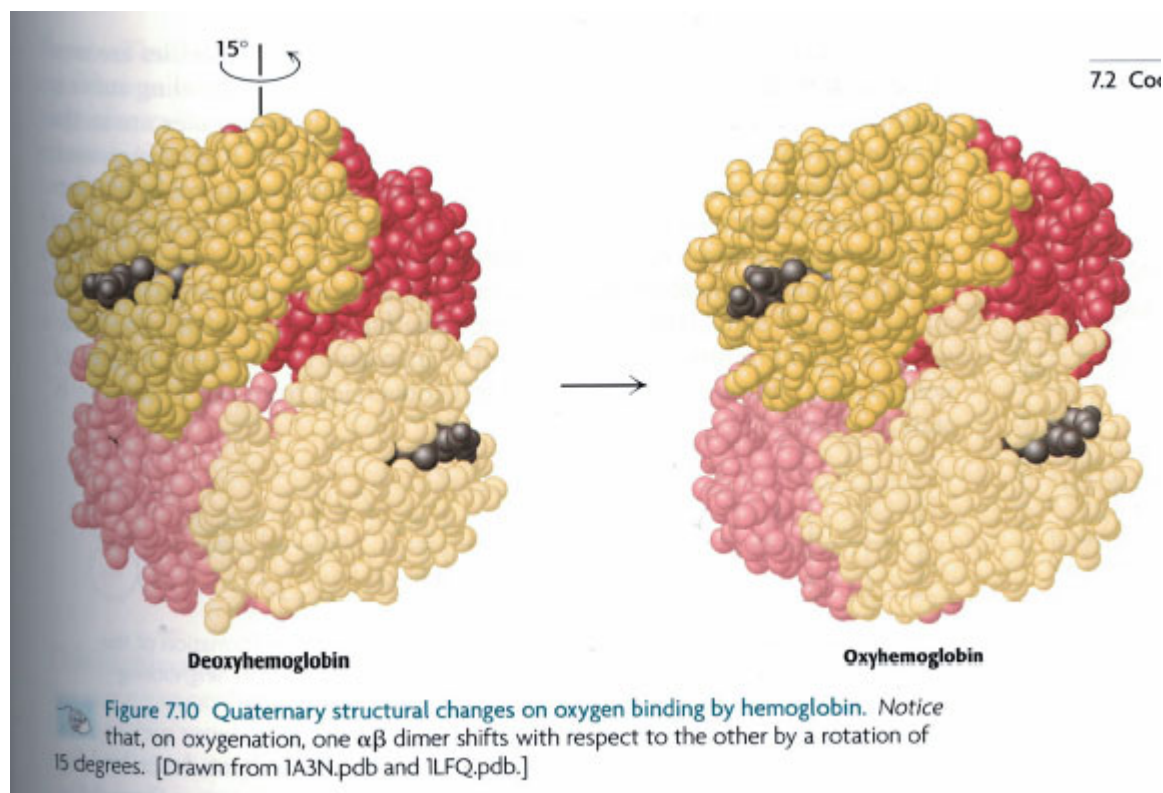
71. A POSA, therefore, would know that two proteins possessing “the same molecular structure” do not necessarily have the same, or even very similar, amino acid sequence. Thus, contrary to Dr. Chaum’s assertion (Ex. 1002 at ¶¶ 50-51, 96, 122-129), a POSA would *not* understand that Dixon’s phrase “molecular structure” necessarily refers to the amino acid sequence.

72. Furthermore, a POSA also would know that two proteins with the same amino acid sequences nonetheless could have distinct three-dimensional structures even under the same conditions. These differences could stem from host cell selection, as well as culture and expression conditions, which were known to markedly affect protein folding and post-translational modification, the latter including glycosylation, phosphorylation, lipidation, methylation, and polypeptide chain truncation due to limited proteolysis. For example, a protein with a given amino acid sequence expressed in *E. coli* may have a different overall structure when it is expressed in a mammalian host cell. Thus, a POSA would not assume that a protein’s amino acid sequence was synonymous with the protein’s molecular structure.

³⁰ Cantu et al., *Thioesterases: A New Perspective Based on Their Primary and Tertiary Structures*, 19 PROTEIN SCI. 1281 (2010).

73. Accordingly, a protein's amino acid sequence *does not* “necessarily drive” or unambiguously “defin[e]” the protein's three-dimensional structure. As just one representative example, human hemoglobin from red blood cells is known to be able to adopt at least two different three-dimensional shapes depending on the “energetic state[] of the molecule.” Ex. 2069 (Mihailescu) at 3773. Specifically, non-oxygenated hemoglobin exists in a so-called tense (“T”) conformational state (“deoxyhemoglobin”). But binding of oxygen (O₂) to hemoglobin in the T state alters the three-dimensional structure of the protein to a relaxed (“R”) conformational state (“oxyhemoglobin”). A pictorial diagram representing the two

molecular structures is reproduced below, showing that “one $\alpha\beta$ dimer shifts with respect to the other by a rotation of 15 degrees”:



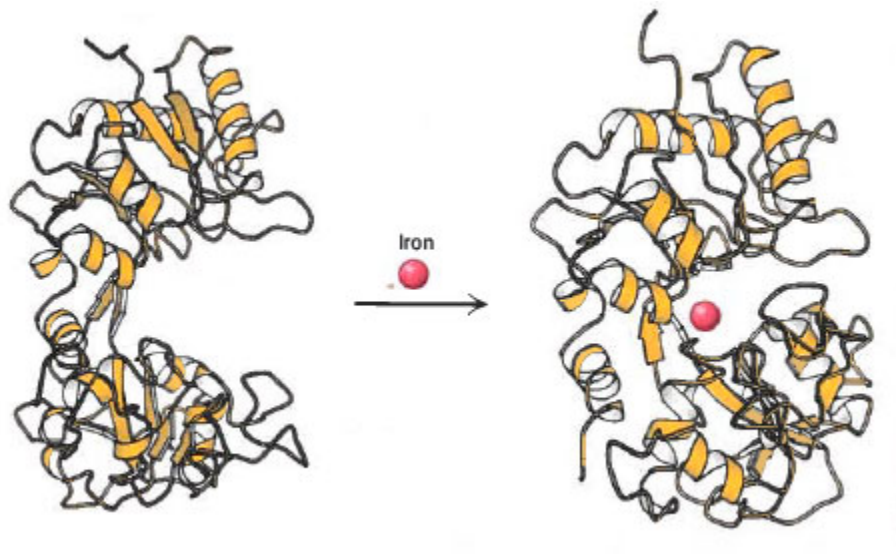
Ex. 2077³¹ at 28, Fig. 7.10.

74. The two different three-dimensional shapes of hemoglobin (T and R) are distinct “molecular structures.” Ex. 2069 (Mihailescu) at 3773. Yet, the primary structure, *i.e.*, the amino acid sequence, of the hemoglobin molecule undeniably remains **unchanged** during the protein’s transition from the T state (a first “molecular structure”) to the R state (a second “molecular structure”). Thus, while

³¹ Excerpts from the textbook by Jeremy M. Berg et al., BIOCHEMISTRY (6th Edn., Freeman, New York, 2007).

the amino acid sequence (*i.e.*, the primary structure) is indeed *a* determinant of the three-dimensional structure of a protein, it is not the *sole* determinant of a protein's three-dimensional structure. *See* the '880 Decision (Ex. 1046) at 51 (citing IPR2021-00880, Ex. 1108 at 32:2-15). Said differently, the primary structure *does not* “necessarily drive” or “defin[e]” the secondary, tertiary, or quaternary structure of a protein. *Contra* the '881 Decision (Ex. 1004) at 32-33; the '880 Decision (Ex. 1046) at 50-51.

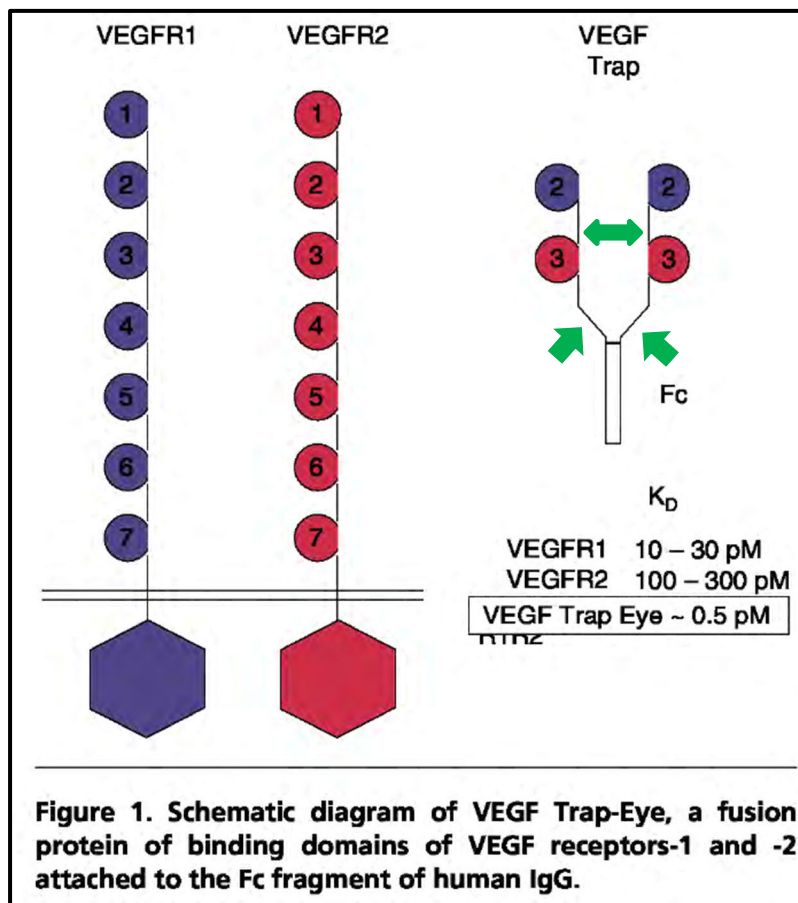
75. Lactoferrin, a globular protein of the transferrin family and a component of the immune system, exhibits similar flexibility in its three-dimensional structure. As illustrated below, like hemoglobin, lactoferrin can also adopt two different three-dimensional structures without any changes to the underlying amino acid sequence:



Ex. 2065 at 5, Fig. 3.3.

76. Therefore, a POSA could understand Dixon's statement that aflibercept and VEGF Trap-Eye "have the same molecular structure" to mean that the two multi-domain fusion proteins share the same three-dimensional structure, such as domain structure, but not necessarily the same amino acid sequence (which may not be identical).

77. Indeed, Dixon discloses that "[s]tructurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Figure 1)." Ex. 1006 at 1575. That cited "Figure 1" from Dixon is reproduced below with added annotations in green:



78. Figure 1 shows VEGF receptors 1 and 2 and the binding domains 2 and 3 that form the VEGF Trap-Eye molecule. Ex. 1006 at 1576. Dixon, therefore, suggests that the “molecular structure” of VEGF Trap-Eye refers to the selection and arrangement of receptor binding domains and a Fc region, not to the amino acid (or encoding nucleic acid) sequence, and certainly *not necessarily* to the amino acid sequence.

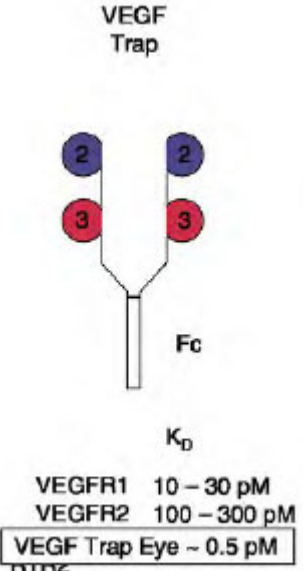
79. As expressly denoted in its caption, Figure 1 of Dixon provides merely a “schematic diagram” of the domain organization of the VEGF Trap-Eye molecule. This kind of schematic diagram is common in scientific literature and provides a cartoon representation of a protein molecule’s structure, including its domain structure. *See, e.g.*, Ex. 2065 at 15, discussed in paragraph 55 above. Unlike an amino acid sequence, where one amino acid unambiguously follows another along the polypeptide chain, a schematic diagram is inevitably imprecise. For example, Dixon’s pictorial diagram connects the binding domains (depicted as equally-sized circles) and the Fc fragment of human IgG (depicted as a rectangular box) with straight lines, representing some sort of linkers between the domains and the Fc fragment. Dixon does not define, or even comment on, the amino acid sequence represented by these lines (annotated by my addition of green arrows in the Figure above). A POSA would understand that Dixon’s Figure 1 encompasses a number of fusion protein molecules containing the named domains connected by linkers. For

at least this reason, Dixon's Figure 1 is *not* limited to representing just a *single* amino acid sequence.

80. The text of Dixon also conveys no information regarding the specific primary, secondary, tertiary, or quaternary structure of VEGF Trap-Eye. The only structural description in Dixon is that “[s]tructurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Figure 1).” Ex. 1006 at 1575. As discussed below in Section X.A.2, the literature provided a range of overlapping amino acid sequences for each of the aforementioned binding domains such that no singular predefined sequence for each domain could be ascertained. In sum, given that Dixon defines VEGF Trap-Eye's structure only by its domains composition, and nothing more, the most reasonable interpretation of Dixon's statement that VEGF Trap-Eye and aflibercept have “the same molecular structure” is that the protein molecules share common domain structures (but *not necessarily* common primary structures).

81. The Holash reference (Ex. 1009) does not cure Dixon's lack of disclosure of the amino acid sequence of VEGF Trap-Eye. Like Dixon, Holash provides merely a schematic diagram of VEGF-Trap_{R1R2}, a fusion protein which “was created by fusing the second Ig domain of VEGFR1 with the third Ig domain

of VEGFR2.” Ex. 1009 at 11393-94. Excerpts from the corresponding schematics in Holash and Dixon are reproduced side-by-side below:

Excerpt from Dixon’s Figure 1 (Ex. 1006)	Excerpt from Holash’s Figure 1A (Ex. 1009)
 VEGF Trap 2 2 3 3 Fc K_D VEGFR1 10 – 30 pM VEGFR2 100 – 300 pM VEGF Trap Eye ~ 0.5 pM	 VEGF Trap R1R2 R1_{D2} R2_{D3} Fc

Holash provides no more specific details about the structure of VEGF Trap-Eye or VEGF-Trap_{R1R2} than Dixon. In particular, Holash provides neither any (i) amino acid sequence information regarding the second Ig domain of VEGFR1 (“R1_{D2}”) or the third Ig domain of VEGFR2 (“R2_{D3}”), nor (ii) information about the linkers connecting the aforementioned domains. Thus, a POSA would understand Holash’s schematic diagram representing domain organization not to be limited to merely a single amino acid sequence.

82. Dr. Chaum opines that a POSA would have known before 2011 that “Regeneron’s VEGF Trap was aflibercept” because Gomez-Manzano (Ex. 1011),

Adis (Ex. 1012), and Rudge 2007 (Ex. 1014) all use the term “aflibercept” and “refer back to Holash and its description of VEGF-TrapR1R2.” Ex. 1002 at ¶¶ 50, 51, 53. In my opinion, Dr. Chaum’s assertion is flawed in view of Holash.

83. Even if it were true that Gomez-Manzano (Ex. 1011), Adis (Ex. 1012), and Rudge 2007 (Ex. 1014) all “refer back to Holash and its description of VEGF-TrapR1R2” (Ex. 1002 at ¶¶ 51, 53), that fact still would not establish that VEGF Trap-Eye (or VEGF Trap for that matter) was known to a POSA to necessarily correspond to the specific amino acid or nucleic acid sequences of the challenged claims. As explained above in paragraph 81, Holash (Ex. 1009) at best provides domain structure information that is not limited to merely a single amino acid sequence. Thus, “refer[ring] back to Holash” (Ex. 1009) does nothing to establish a particular amino acid sequence for Dixon’s VEGF Trap-Eye molecule.

84. Therefore, while the term “molecular structure” generally can be used in the art to refer to the primary, or secondary, or domain, or tertiary, or quaternary structure of a protein, in view of Dixon’s focused discussion of VEGF Trap-Eye in terms of its domain structures specifically (Figure 1), the most reasonable interpretation is to attribute Dixon’s “the same molecular structure” phrase to *the same domain structures* discussed therein. In other words, it is certainly not the *only* reading of Dixon that “molecular structure” must mean amino acid sequence; nor is it even the most plausible one.

2. A POSA would understand that a given protein domain structure does not necessarily correspond to a single amino acid sequence

85. As discussed above in paragraph 55, a domain structure in a protein is defined as a region that can fold and function nearly independently from the rest of the protein molecule. Furthermore, even distinct primary structures can result in the same domain structure, particularly when those primary structures contain analogous amino acid residues (*i.e.*, those of similar charge, hydrophobicity, and size) at key positions in the polypeptide chain.

86. Indeed, the literature provides *more than just one* amino acid sequence comprising VEGFR1 domain 2. Below is a chart summarizing various amino acid sequences of VEGFR1 domain 2, as defined by different literature sources:

Literature Source	VEGFR1 (Flt-1) domain 2		
	Starting Amino Acid	Ending Amino Acid	Domain Length
Davis-Smyth et al. 1996 (Ex. 2078) ³²	134 Pro (P)	226 Thr (T)	93 residues
UNIPROT P17948 (Ex. 2079) ³³ (Ex. 2080) ³⁴	151 Gly (G)	214 His (H)	64 residues

³² Davis-Smyth et al., *The Second Immunoglobulin-like Domain of the VEGF Tyrosine Kinase Receptor Flt-1 Determines Ligand Binding and May Initiate a Signal Transduction Cascade*, 15 EMBO J. 4919 (1996) (“Davis-Smyth”).

³³ P17948 VEGFR1_Human, UNIPROT, <https://www.uniprot.org/uniprotkb/P17948/entry> (“UNIPROT P17948”).

³⁴ P17948 VEGFR1_Human, Entry Version 140 (txt), UNIPROT (Jan. 11, 2011), <https://rest.uniprot.org/unisave/P17948?format=txt&versions=140> (“UNIPROT P37948 v140”).

Wiesmann et al. 1997 (Ex. 2081) ³⁵	129 Ser (S)	229 Ile (I)	101 residues
Papadopoulos (Ex. 1036) ³⁶	27 Gly (G)	126 Asp (D)	100 residues

87. In determining the amino acid sequence comprising VEGFR1 domain 2 disclosed by Davis-Smyth (Ex. 2078), I reviewed the sequence information provided by Davis-Smyth's Figure 1, which is an "[a]lignment of the E[xtracellular]C[ellular]D[omain]s of Flt-1, KDR and Flt-4" (where "Flt-1" refers to VEGFR1, "KDR" stands for kinase domain receptor and refers to VEGFR2, and

³⁵ Wiesmann et al., *Crystal Structure at 1.7 Å Resolution of VEGF in Complex with Domain 2 of the Flt-1 Receptor*, 91 CELL 695 (1997) ("Wiesmann").

³⁶ U.S. Patent No. 7,374,758 B2 ("Papadopoulos").

“Flt-4” refers to VEGFR3). Ex. 2078 at 4920. An excerpt of Figure 1 of Davis-Smyth is reproduced below starting at position 1:

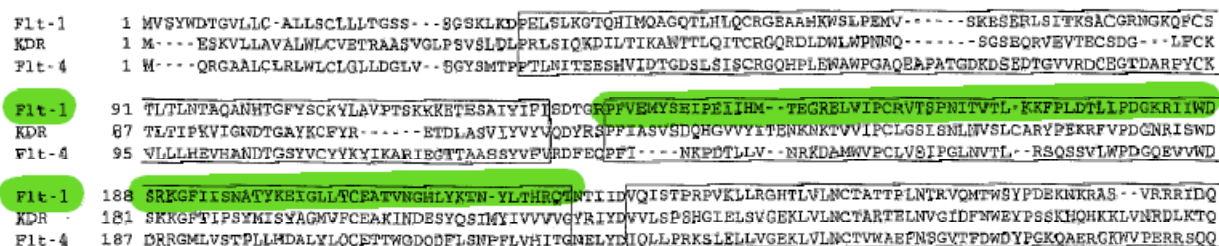
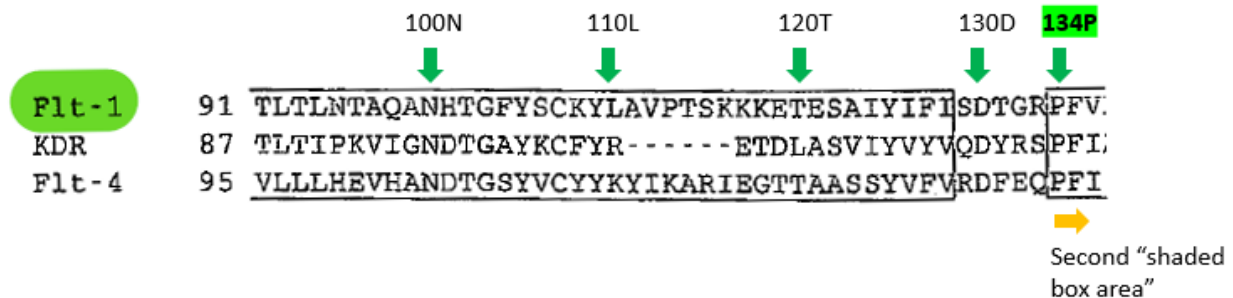


Fig. 1. Alignment of the ECDs of Flt-1, KDR and Flt-4. The seven Ig-like domains are shown as shaded boxed areas. Note that the amino acid numbering begins with position 1 at the first Met of the signal peptide sequence.

As expressly denoted in the figure caption, each of the “boxed areas” represents one of “seven Ig-like domains” of the three proteins aligned, with “Flt-1” representing VEGFR1. Therefore, the stretch of amino acid sequence comprising VEGFR1 domain 2 is the “Flt-1” sequence contained in the second box (annotated by my addition of green highlight above). To determine where VEGFR1 domain 2 begins starting from Flt-1 position 91, a threonine (“T” using a one-letter code for amino acids henceforth unless stated otherwise), I counted the position of the first amino acid residue of Flt-1 contained in this second box. An enlarged and annotated

excerpt below shows that the first amino acid residue of VEGFR1 domain 2, a proline (“P”), is located at position 134:



To determine where VEGFR1 domain 2 ends starting from Flt-1 position 188, a serine (“S”), I counted the position of the last amino acid residue contained in this second box. The “-” was not counted as an amino acid residue position. An enlarged and annotated excerpt below shows that the last amino acid residue of VEGFR1 domain 2, a threonine (“T”), is located at position 226:

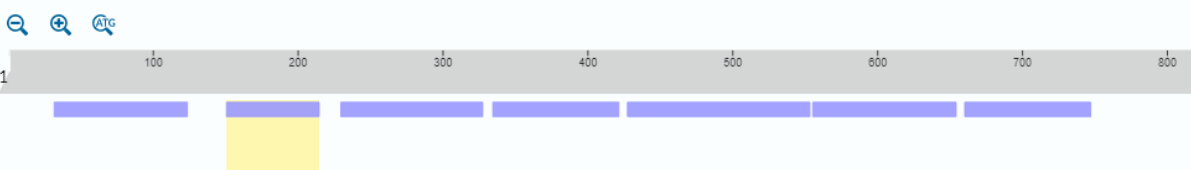


Based on the starting and ending positions extracted from Davis-Smyth, I calculated the length of the stretch of amino acid sequence comprising VEGFR1 domain 2 to be 93 amino acid residues (226 - 134 + 1).

88. In determining the amino acid sequence comprising VEGFR1 domain 2 disclosed by UNIPROT P17948 (Ex. 2079), I reviewed the “Family & Domains” section of the website. This section annotates the seven domains of VEGFR1 as “Ig-like C2-type” 1 through 7. When I expanded the description for VEGFR1 domain 2 (“Ig-like C2 type 2”), the annotation indicates that the domain spans amino acid positions “151-214” and provides the corresponding amino acid sequence of the domain. Ex. 2079 at 9. Taken together, this annotation indicates that the VEGFR1 domain 2 starts at position 151, a glycine (“G”), and ends at position 214, a histidine (“H”). An excerpt of the domain annotation information from UNIPROT P17948 is reproduced below:

Family & Domainsⁱ

Features
Showing features for domain¹, region¹, compositional bias¹.



TYPE	ID	POSITION(S)	DESCRIPTION
Domain			
▶ Domain		32-123	Ig-like C2-type 1
▼ Domain		151-214	Ig-like C2-type 2
Sequence: GRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGH			
▶ Domain		230-327	Ig-like C2-type 3
▶ Domain		335-421	Ig-like C2-type 4
▶ Domain		428-553	Ig-like C2-type 5
▶ Domain		556-654	Ig-like C2-type 6
▶ Domain		661-747	Ig-like C2-type 7
▶ Domain		827-1158	Protein kinase PROSITE-ProRule Annotation

Id. Based on the starting and ending positions extracted from UNIPROT P17948, I calculated the length of the stretch of amino acid sequence comprising VEGFR1 domain 2 to be 64 amino acid residues (214 - 151 + 1).

89. I have confirmed that this UNIPROT annotation of VEGFR1 domain 2 is consistent with an annotation found in an earlier version of the same UNIPROT entry, which was available before the priority date of the '681 Patent (January 13, 2011). UNIPROT P37948 v140, dated January 11, 2011, provides the following annotation:

FT	SIGNAL	1	26	
FT	CHAIN	27	1338	Vascular endothelial growth factor
FT				receptor 1.
FT				/FTId=PRO_0000016768.
FT	TOPO_DOM	27	758	Extracellular (Potential).
FT	TRANSMEM	759	780	Helical; (Potential).
FT	TOPO_DOM	781	1338	Cytoplasmic (Potential).
FT	DOMAIN	32	123	Ig-like C2-type 1.
FT	DOMAIN	151	214	Ig-like C2-type 2.
FT	DOMAIN	230	327	Ig-like C2-type 3.
FT	DOMAIN	335	421	Ig-like C2-type 4.
FT	DOMAIN	428	553	Ig-like C2-type 5.
FT	DOMAIN	556	654	Ig-like C2-type 6.
FT	DOMAIN	661	747	Ig-like C2-type 7.
FT	DOMAIN	827	1158	Protein kinase.

Ex. 2080 at 3. The highlighted entry “DOMAIN ... Ig-like C2-type 2” indicates a VEGFR1 domain 2 spanning the same amino acid positions 151 to 214 as discussed above in paragraph 88. Therefore, the same stretch of amino acid sequence of 64 amino acid residues (214 - 151 + 1) comprising VEGFR1 domain 2 was known to a POSA before the priority date of the '681 Patent (January 13, 2011).

90. Wiesmann (Ex. 2081) discloses a different set of starting and ending amino acid residues of VEGFR1 domain 2. Under the “experimental procedures” section, Wiesmann provides that “[f]or expression of domain 2 alone, residues 129-229 of Flt-1 were constructed in a phagemid vector [*i.e.*, a cloning vector having both bacteriophage and plasmid properties] under the control of an alkaline phosphatase promoter and stII secretion signal.” Ex. 2081 at 702. Wiesmann further provides a portion of the amino acid sequence of Flt-1 as Figure 7, reproduced below:

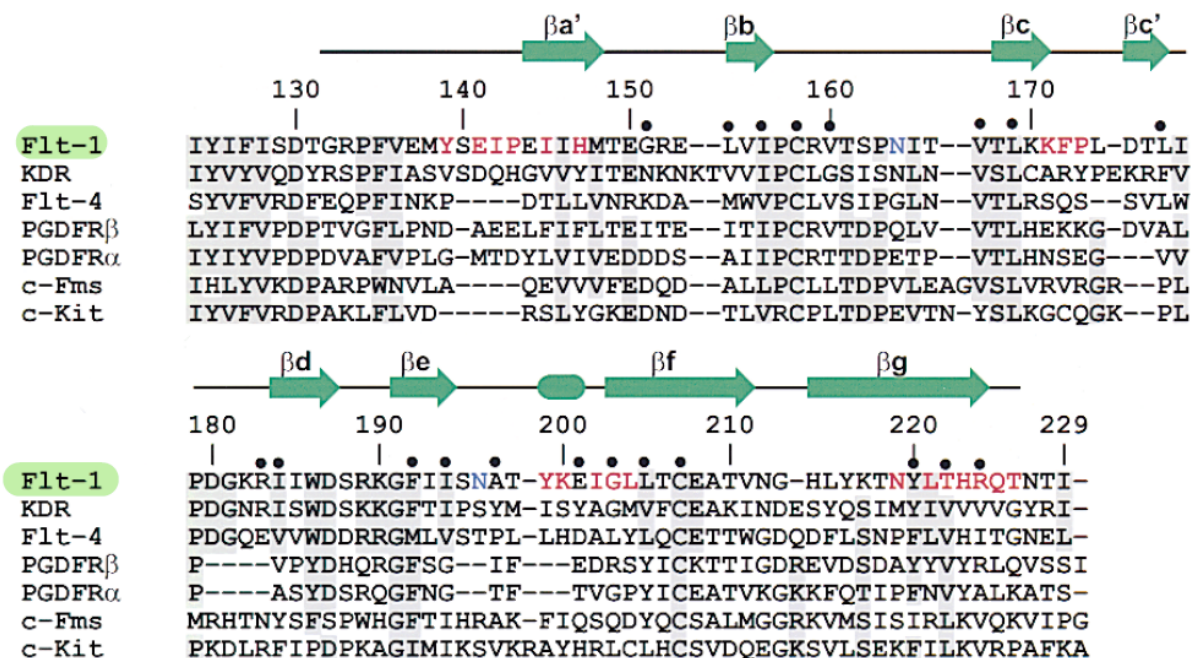


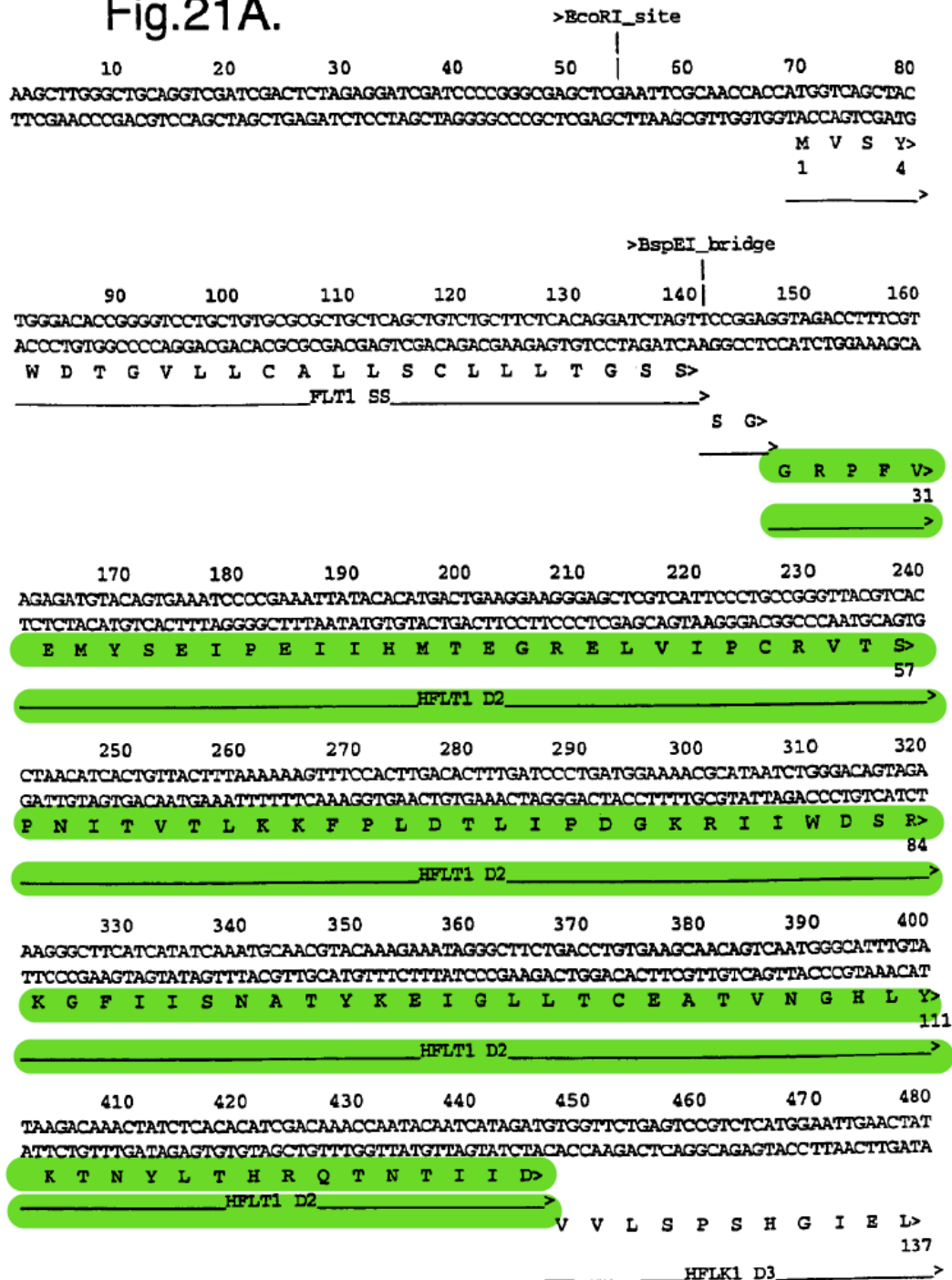
Figure 7. Sequence Alignment of Domain 2 of the Members of the PDGF Receptor Family

Ex. 2081 at 701. Taken together, the first amino acid residue of VEGFR1 domain 2 is a serine (S) located at position 129 of the Flt-1 sequence (*i.e.*, one residue to the left of “D”, marked as “130”), while the last amino acid residue is an isoleucine (I)

located at position 229 of the Flt-1 sequence (*i.e.*, the residue marked as “229”). Therefore, Wiesmann’s amino acid sequence comprising VEGFR1 domain 2 has a length of 101 amino acid residues ($229 - 129 + 1$).

91. I further reviewed the amino acid sequence comprising VEGFR1 domain 2 disclosed by Papadopoulos. Ex. 1036. In Papadopoulos, the relevant amino acid sequence information is presented as a part of a fusion protein “Flt1D2.FlklD3.FcΔC1(a)” having SEQ ID NO:11. Ex. 1036 at 10:4-6. This amino acid sequence is annotated in Figure 21A and is reproduced below:

Fig.21A.



Ex. 1036 at p. 33. In the excerpt depicted above, “HFLT1 D2” represents VEGFR1 domain 2. The corresponding stretch of the amino acid sequence relevant to my analysis is highlighted in green above. To determine where VEGFR1 domain 2

112K
↓
K T N Y L T H R Q T N T I I D>
HFLT1 D2

Exhibit 2057
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Based on the starting and ending positions extracted from Papadopoulos, I calculated the length of the stretch of the amino acid sequence disclosed as encoding VEGFR1 domain 2 to be 100 amino acid residues (126 - 27 + 1).

92. The literature also provides *more than just one* amino acid sequence comprising VEGFR2 domain 3. Below is a chart summarizing various amino acid sequences of VEGFR2 domain 3, as defined by different literature sources:

Literature Source	VEGFR2 (KDR) domain 3		
	Starting Amino Acid	Ending Amino Acid	Domain Length
Davis-Smyth et al. 1996 (Ex. 2078) ³⁸	226 Val (V)	327 Lys (K)	102 residues
Lu et al. 2000 (Ex. 2082) ³⁹	221 Tyr (Y)	334 Ser (S)	114 residues
Franklin et al. 2011 (Ex. 2083) ⁴⁰	220 Gly (G)	328 Ser (S)	109 residues
UNIPROT P35968 (Ex. 2084) ⁴¹ (Ex. 2085) ⁴²	224 Tyr (Y)	320 Thr (T)	97 residues

³⁸ Davis-Smyth et al., *The Second Immunoglobulin-like Domain of the VEGF Tyrosine Kinase Receptor Flt-1 Determines Ligand Binding and May Initiate a Signal Transduction Cascade*, 15 EMBO J. 4919 (1996) (“Davis-Smyth”).

³⁹ Lu et al., *Identification of the Residues in the Extracellular Region of KDR Important for Interaction with Vascular Endothelial Growth Factor and Neutralizing Anti-KDR Antibodies*, 275 J. BIOL CHEM. 14321 (2000) (“Lu”).

⁴⁰ Franklin et al., *The Structural Basis for the Function of Two Anti-VEGF Receptor 2 Antibodies*, 19 STRUCTURE 1097 (2011) (“Franklin”).

⁴¹ P35968 VGFR2_Human, UNIPROT, <https://www.uniprot.org/uniprotkb/P35968/entry> (“UNIPROT P35968”).

⁴² P35968 VGFR2_Human, Entry Version 127 (txt), UNIPROT (Jan. 11, 2011), <https://rest.uniprot.org/unisave/P35968?format=txt&versions=127> (“UNIPROT P35968 v127”).

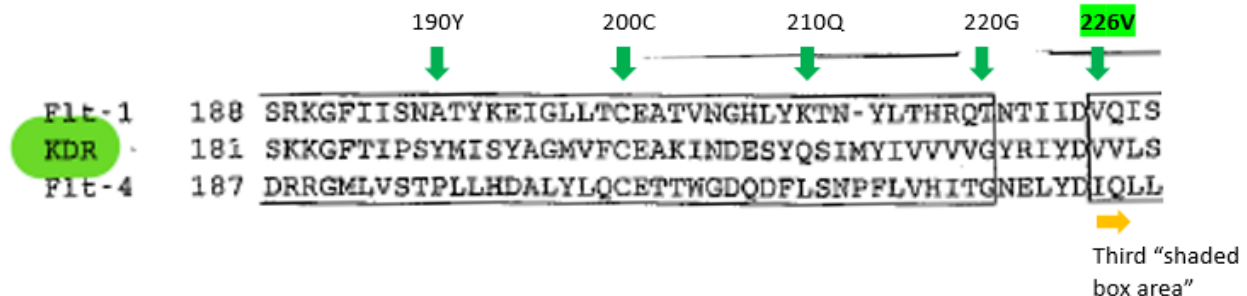
93. In determining the amino acid sequence comprising VEGFR2 domain 3 disclosed by Davis-Smyth (Ex. 2078), I reviewed the sequence information provided by the same Figure 1 discussed above in paragraph 87, which is an “[a]lignment of the E[xtracellular]C[ellular]D[omain]s of Flt-1, KDR and Flt-4.” Ex. 2078 at 4920. An excerpt of Figure 1 of Davis-Smyth is reproduced below starting at position 1:

Flt-1	1	MVSYWDTGVLLC-ALLSCLLLTGSS--SGSKLKDFELSLKGTQHIMQAGQTLHLQCRGEAAHKWSLPEMV-----SKESERLSYTKSACGRNGKQFCS
KDR	1	M----ESKVLIAVALMLCVETRAASVGLPSVSLDLPRLSIQKDILTIKANTTLQITCRGQRDLDLWLPNNQ-----SGSEQRVEVTECSDG--LPCK
Flt-4	1	M----QRGAALCLRLMLCLGLLDGLV--SGYSMTPTLNITEESHVIDTGDLSLSISCRGQHPLEWANPGAQEPATGDKDSEDGTGVVRDCEGTARPYCK
Flt-1	91	TLTLNTAQANHTGFYSCKYLAVPTSKKKEESALYIFISDTGRPFVEMYSEIPEIITHM--TEGRELVIPCRVTSFNITVTTL-KKFPILDTLIPDGKRIIWD
KDR	87	TLTIPKVIQNDTGAYKCFYR-----ETDLASVIYVYQDYRSPIASVSDQHGVIYITENKNTVVIPCLGSTISNLNLSLCARYPEKRFVPDGNRISWD
Flt-4	95	VLLLEHVHNDTGSYVCYYKIKARIEGTTAASSYVFURDFEQPFI---NKPDTLLV--NRKDAMWVPCLVSIPLNVTLL--RSQSSVLWPDGQSVVWD
Flt-1	188	SRKGFIIISNATYKEIGLLTCEATVNGHLYKTN-YLTHRQTNTIIDVQISTRRPVKLLRCHTLVNLCTATPLNTRVQMTWSYPDEKMKRAS--VRRRIDQ
KDR	181	SKKGFITPSYKISYAGMVFCEAKINDESYQSIMYIVVVVGYRIYIVVLSPSHGIELSVGEKLVNLCTARTELVNGIDFNWEYFSSKHQHKLVNRDLKTQ
Flt-4	187	DRRGMLVSTPLLDALYLQCETTWGDQDFLSNPFPLVHITGNELVNIQLLPKSLLELVGEKLVNLCTVWAEFNSGVTFDWDYFGKQAEKGVFERRSQ
Flt-1	285	SNSHANIFYSVLTIDKMKQNDKGLVTCRVRSQPSFKSVNTSVHIVDKAFITVKHRRQQVLETVAGKRSYRLSHKVKRFPSPEVVWLKDGLPATEKSARYL
KDR	281	SGSEMKKPLSLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHENFFVAFGSGMESLVEATVGER-VRIPAKYLGYPPPEIKWYKNGIPLESN--HTI
Flt-4	287	THTELS--SILTIHNVSQHDLGSYVCKANNGIORPRESTEVIIVHENPFISVEWLKGFILKATAGDELVKLVKLAAYFPPEFQWYKDGKALSGR--H--

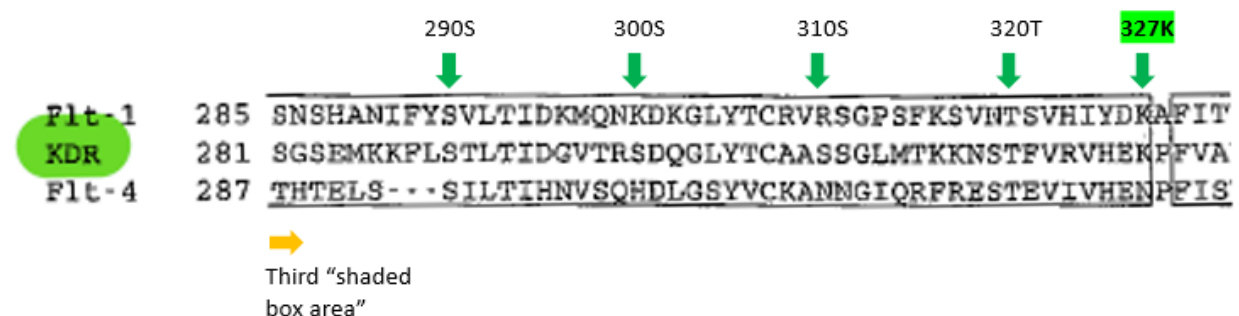
Fig. 1. Alignment of the ECDs of Flt-1, KDR and Flt-4. The seven Ig-like domains are shown as shaded boxed areas. Note that the amino acid numbering begins with position 1 at the first Met of the signal peptide sequence.

As expressly denoted in the figure caption, each of the “boxed areas” represents one of “seven Ig-like domains” of the three proteins aligned. In the excerpt above, the “KDR” (kinase domain receptor) represents VEGFR2. Therefore, the stretch of the amino acid sequence comprising VEGFR2 domain 3 is the “KDR” amino acid sequence contained in the third box (annotated by my addition of green highlight above). To determine where VEGFR2 domain 3 begins starting from KDR position 181, which is a serine (“S”), I counted the position of the first amino acid residue of KDR contained in this third box. An enlarged and annotated excerpt below shows

that the first amino acid residue of VEGFR2 domain 3, a valine (“V”), is located at position 226:



To determine where VEGFR2 domain 3 ends starting from KDR position 281, which is a serine (“S”), I counted the position of the last amino residue contained in this third box. An enlarged and annotated excerpt below shows that the last amino acid residue of VEGFR2 domain 3, a lysine (“K”), is located at position 327:



Based on the starting and ending positions extracted from Davis-Smyth, I calculated the length of the stretch of amino acid sequence comprising VEGFR2 domain 3 to be 102 amino acid residues (327 - 226 + 1).

94. Lu (Ex. 2082) discloses a different set of starting and ending amino acid residues of VEGFR2 domain 3. Under the “experimental procedures” section, Lu provides a “KDR domain 3 (from Tyr²²¹ to Ser³³⁴).” Ex. 2082 at 14322. Based on this disclosure, the first amino acid residue of VEGFR2 domain 3 is a tyrosine (“Y”) located at position 221 and the last amino acid residue is a serine (“S”) located at position 334. Therefore, Lu’s amino acid sequence comprising VEGFR2 domain 3 has a length of 114 amino acid residues ($334 - 221 + 1$).

95. Franklin (Ex. 2083) discloses yet another set of starting and ending amino acid residues of VEGFR2 domain 3. Under the “experimental procedures” section, Franklin provides a “KDR domain 3[] containing residues Gly220-Ser328 of human KDR.” Ex. 2083 at 1104. Based on this disclosure, the first amino acid residue of VEGFR2 domain 3 is a glycine (“G”) located at position 220 and the last amino acid residue is a serine (“S”) located at position 328. Therefore, Franklin’s amino acid sequence comprising VEGFR2 domain 3 has a length of 109 amino acid residues ($328 - 220 + 1$).

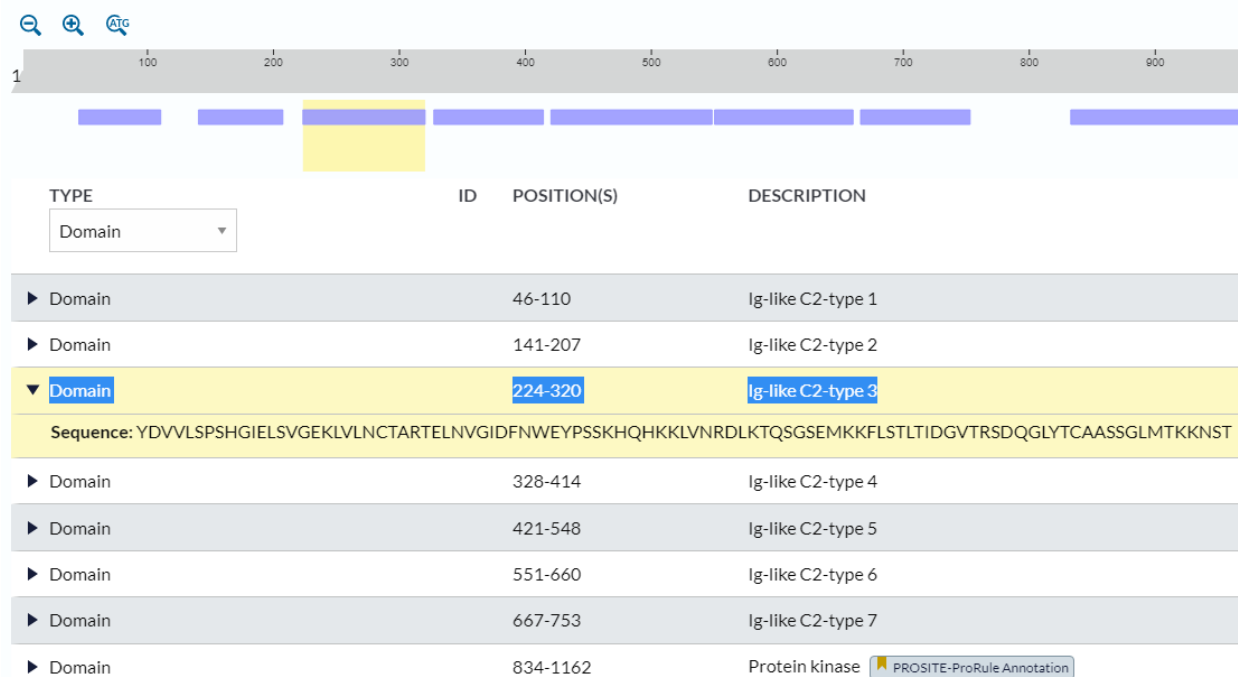
96. In determining the amino acid sequence comprising VEGFR2 domain 3 disclosed by UNIPROT P35968 (Ex. 2084), I reviewed the “Family & Domains” section of the website. This section annotates the seven domains of VEGFR2 as “Ig-like C2-type” 1 through 7. When I expanded the description for VEGFR2 domain 3 (“Ig-like C2 type 3”), the annotation indicates that the domain spans amino acid

positions “224-320” and provides the corresponding amino acid sequence of the domain. Ex. 2084 at 12. Taken together, this annotation indicates that the VEGFR2 domain 3 starts at position 224, a tyrosine (“Y”), and ends at position 320, a threonine (“T”). An excerpt of the domain annotation information from UNIPROT P35968 is reproduced below:

Family & Domainsⁱ

Features

Showing features for domainⁱ, regionⁱ, compositional biasⁱ.



Id. Based on the starting and ending positions extracted from UNIPROT P35968, I calculated the length of the stretch of amino acid sequence comprising VEGFR2 domain 3 to be 97 amino acid residues (320 - 224 + 1).

97. I have confirmed that this UNIPROT annotation of VEGFR2 domain 3 is consistent with an annotation found in an earlier version of the same UNIPROT

entry, which was available before the priority date of the '681 Patent (January 13, 2011). UNIPROT P35968 v127, dated January 11, 2011, provides the following annotation:

FT	SIGNAL	1	19	Potential.
FT	CHAIN	20	1356	Vascular endothelial growth factor
FT				receptor 2.
FT				/FTId=PRO_0000016771.
FT	TOPO_DOM	20	764	Extracellular (Potential).
FT	TRANSMEM	765	789	Helical; (Potential).
FT	TOPO_DOM	790	1356	Cytoplasmic (Potential).
FT	DOMAIN	46	110	Ig-like C2-type 1.
FT	DOMAIN	141	207	Ig-like C2-type 2.
FT	DOMAIN	224	320	Ig-like C2-type 3.
FT	DOMAIN	328	414	Ig-like C2-type 4.
FT	DOMAIN	421	548	Ig-like C2-type 5.
FT	DOMAIN	551	660	Ig-like C2-type 6.
FT	DOMAIN	667	753	Ig-like C2-type 7.

Ex. 2085 at 3. The highlighted entry “DOMAIN ... Ig-like C2-type 3” indicates a VEGFR2 domain 3 spanning the same amino acid positions 224 to 320 as discussed above in paragraph 96. Therefore, the same stretch of the amino acid sequence of 97 amino acid residues (320 - 224 + 1) comprising VEGFR2 domain 3 was known to a POSA before the priority date of the '681 Patent (January 13, 2011).

98. The charts above in paragraphs 86 and 92 demonstrate that the amino acid sequences encoding VEGFR1 domain 2 contain overlapping regions of the underlying full sequence of VEGFR1 and that they do not necessarily start and/or end at the same amino acid residue position—*i.e.*, that they have different primary structures. The same can be said for the amino acid sequences encoding VEGFR2

domain 3. The observations presented above also illustrate that amino acid sequences of variable lengths can define the same domain structure.

99. Therefore, based on the structural information provided in Dixon—*i.e.*, that VEGF Trap-Eye is “a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment” (Ex. 1006 at 1575)—a POSA could generate no fewer than sixteen ($4 \times 4 = 16$) different amino acid sequences⁴³ that would satisfy this description based on the at least four (4) amino acid sequences for VEGFR1 domain 2 and the at least four (4) amino acid sequences for VEGFR2 domain 3. The structural information from Holash—*i.e.*, that VEGF-Trap_{R1R2} “was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2,” (Ex. 1009 at 11393-94)—similarly would allow a POSA to generate at least sixteen (16) different amino acid sequences that would each satisfy the description.

100. In my opinion, a POSA would not know, before the priority date of the '681 Patent (January 13, 2011), which particular sequence out of the at least sixteen ($4 \times 4 = 16$) different amino acid sequences would produce an intact, properly

⁴³ Even if Petitioner or Dr. Chaum argues that the amino acid sequence of VEGFR2 domain 3 disclosed by Franklin (Ex. 2083) was not available prior to January 2011, there would still be no fewer than twelve ($4 \times 3 = 12$) different amino acid sequences that would each satisfy the domain structure description of VEGF Trap-Eye provided in Dixon.

folded, and biologically competent *in vivo* fusion protein. It also cannot be said that the claimed amino acid sequence is a natural result of the disclosure of Dixon (or Holash) because the domain structure description naturally and inevitably lends itself to more than one amino acid sequences. Thus, without knowledge about the specific sequence of VEGF Trap-Eye before the priority date, the mere possibility that one of those sequences could be VEGF Trap-Eye cannot render the claimed sequence inherently obvious.

101. The observation that multiple amino acid sequences can encode the same domain structure is consistent with prior art studies demonstrating that proteins can tolerate amino acid substitutions at certain positions without any changes in the protein's structure or function. Ex. 2086⁴⁴ at 1306. For example, researchers studying approximately 1500 single amino acid substitutions in 142 positions in the *lac* repressor protein found that “about one-half of all substitutions were phenotypically silent [*i.e.*, resulted in no change in observable characteristics of the protein].” *Id.* In particular, amino acid residues at positions where many different, non-conserved substitutions were tolerated appeared to “play little or no role in structure and function [of the protein].” *Id.*

⁴⁴ Bowie et al., *Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions*, 247 SCI. 1306 (1990).

102. In view of the foregoing, a POSA would understand that a given domain structure does not necessarily stem from, or correspond to, only one primary structure. Accordingly, given the domain structural information provided in Dixon, a POSA could not definitively reverse engineer just a single amino acid sequence of VEGF Trap-Eye, let alone the amino acid sequence claimed in the '681 Patent.

3. A POSA would understand that VEGF Trap-Eye could encompass a genus of amino acid sequences

103. The structural information identified in Dixon—*i.e.*, that VEGF Trap-Eye is “a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment” (Ex. 1006 at 1575)—does not distinguish VEGF Trap-Eye from any other protein comprising a human VEGFR1 domain 2, a human VEGFR2 domain 3, and a Fc region of a human immunoglobulin (IgG). In other words, based on the teaching of the prior art as a whole, the disclosure in Dixon would be understood by a POSA to refer to a *genus* of protein sequences.

104. Dr. Chaum cites to Dixon’s statement that “[o]ne promising new drug is aflibercept (VEGF Trap-Eye)” (Ex. 1006, 1573) to opine that “Regeneron’s VEGF Trap was aflibercept.” Ex. 1002 at ¶¶ 50-51. However, this statement in Dixon does not change my opinion that VEGF Trap-Eye could encompass a genus of protein sequences, as outlined above in Sections X.A.1 and X.A.2. Not only has Dr. Chaum conflated VEGF Trap with VEGF Trap-Eye, but such an isolated reading ignores

multiple other disclosures in Dixon discussed in paragraphs 37-38 above and in other references indicating that VEGF Trap-Eye and aflibercept are two different drugs.

105. By the early 2000s, Regeneron had developed, tested, and published on a variety of engineered VEGF fusion proteins that it called “VEGF Trap.” *See, e.g.*, Ex. 1009 (Holash) at 11394 Fig. 1 (disclosing VEGF Trap_{parental}, VEGF Trap_{ΔB1}, VEGF Trap_{ΔB2}, and VEGF Trap_{R1R2}). Even the term “VEGF Trap_{R1R2},” which is obviously more narrow than “VEGF Trap,” was known in the art to be a genus of protein sequences (as described in the following paragraphs), any species of which could satisfy Dixon’s reference to the “molecular structure,” but would not necessarily possess the same amino acid sequence as recited in the challenged claims of the ’681 Patent.

106. The Papadopoulos ’758 Patent, an issued Regeneron patent, disclosed at least two fusion proteins it described as “R1R2.” *See* Ex. 1036⁴⁵ at 10:4-17, 26:5-20. Both of Papadopoulos’s disclosed protein sequences comprised a human VEGF-R1 domain 2, a human VEGF-R2 domain 3, and a portion of the Fc region from an IgG1 antibody; therefore, they would qualify as a “R1R2” VEGF Trap despite having different respective amino acid sequences. *Id.*; *see also id.* at 39:25-90:65. More specifically, Fig. 21A-C and SEQ ID NO:11 & SEQ ID NO:12 disclose the

⁴⁵ U.S. Patent No. 7,374,758 B2.

nucleic acid and amino acid sequences for Flt1D2.Flk1D3.FcΔC1(a). *Id.* at 10:4-6; pp. 33-35, Figs. 21A-C. Although the '758 Patent calls this protein sequence "R1R2" (Ex. 1036 at 26:13-19), this disclosed VEGF Trap amino acid sequence does not satisfy the recited sequence limitations of the '681 Patent.

107. A protein-protein sequence alignment between SEQ ID NO:12 of Papadopoulos (Ex. 1036 at pp. 33-35, Figs. 21A-C) and SEQ ID NO:2 of the '681 Patent (Ex. 1001 at 18:18-28) demonstrates that the "R1R2" amino acid sequence of

Papadopoulos is not the same as the amino acid sequence in the challenged claims of the '681 Patent. The sequences are aligned below:⁴⁶

Score	Expect	Method	Identities	Positives	Gaps	Frame
930 bits(2404)	0.0()	Compositional matrix adjust.	455/461(99%)	455/461(98%)	6/461(1%)	
Query 1	MVSYWDTGVLLCALLSCLLLTGSSSG---	GRPFVEMYSEIPEIIHMTGRELVIPCRVTS	57			
Sbjct 1	MVSYWDTGVLLCALLSCLLLTGSSSGSDT	GRPFVEMYSEIPEIIHMTGRELVIPCRVTS	60			
Query 58	PNITVTLKKFPLDTLIPDGKRIIWDNRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYT		117			
Sbjct 61	PNITVTLKKFPLDTLIPDGKRIIWDNRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYT		120			
Query 118	HRQTNTIIDVVLSPSHGIELSVGEKLVNLCTARTELNVGIDFNWEYPSSKHQHKLVNRD		177			
Sbjct 121	HRQTNTIIDVVLSPSHGIELSVGEKLVNLCTARTELNVGIDFNWEYPSSKHQHKLVNRD		180			
Query 178	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKGPGDKTHTC		237			
Sbjct 181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK---DKTHTC		237			
Query 238	PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN		297			
Sbjct 238	PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN		297			
Query 298	AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP		357			
Sbjct 298	AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP		357			
Query 358	QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFL		417			
Sbjct 358	QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFL		417			
Query 418	YSKLTVDKSRWQGNVFSCSVMHEALHNHYTQKSLSLSPGK		458			
Sbjct 418	YSKLTVDKSRWQGNVFSCSVMHEALHNHYTQKSLSLSPGK		458			

The “Query” sequence above represents SEQ ID NO:12 of Papadopoulos; the “S[u]bj[e]ct” sequence represents SEQ ID NO:2 of the '681 Patent; and the sequence positioned in-between denotes amino acid residues that are common between the two aligned sequences. Each amino acid is represented using a single-letter code, and dashes (“-”) signify that the corresponding amino acid from the counterpart sequence does not exist. The sequence comparison, therefore, establishes that the

⁴⁶ I understand that the blastp suite of the BLAST® computer program with default alignment parameters was used to create the sequence comparison. It is available at <https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins> (“Align two or more sequences”).

two sequences differ from each other by six amino acid residues. In particular, SEQ ID NO:12 of Papadopoulos (i) lacks three amino acid residues, “SDT” (serine-aspartic acid-threonine), that are found in SEQ ID NO:2 of the ’681 Patent; and (ii) contains three additional amino acid residues, “GPG” (glycine-proline-glycine), that are not present in SEQ ID NO:2 of the ’681 Patent.

108. A POSA would, therefore, understand that the Papadopoulos ’758 Patent discloses a VEGF Trap “R1R2” amino acid sequence (Ex. 1036 at 26:13-15) that does *not* satisfy the recited sequence limitations of the ’681 Patent.

109. Likewise, Dix (Ex. 1037)⁴⁷ discloses a nucleic acid sequence SEQ ID NO:1 and an amino acid sequence SEQ ID NO:2 (Ex. 1037 at pp. 7-9), which correspond to a different disclosed VEGF Trap amino acid sequence that does not satisfy the sequence limitations of the challenged claims of the ’681 Patent. A

⁴⁷ U.S. Patent Application Publication No. 2006/0217311 A1 (“Dix”).

protein-protein sequence alignment between SEQ ID NO:2 of Dix and SEQ ID NO:2 of the '681 Patent reveals the differences:

Score	Expect	Method	Identities	Positives	Gaps	Frame
930 bits(2404)	0.0()	Compositional matrix adjust.	455/461(99%)	455/461(98%)	6/461(1%)	
Query 1	MVSYWDTGVLLCALLSCLLLTGSSSG---	GRPFVEMYSEIPEIIHMTGRELVIPCRVTS	57			
Sbjct 1	MVSYWDTGVLLCALLSCLLLTGSSSGSDT	GRPFVEMYSEIPEIIHMTGRELVIPCRVTS	60			
Query 58	PNITVTLKKFPLDTLIPDGKRIIWSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYT	117				
Sbjct 61	PNITVTLKKFPLDTLIPDGKRIIWSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYT	120				
Query 118	HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSSKHQHKLVNRD	177				
Sbjct 121	HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSSKHQHKLVNRD	180				
Query 178	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKGP	237				
Sbjct 181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK---	237				
Query 238	PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN	297				
Sbjct 238	PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN	297				
Query 298	AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREP	357				
Sbjct 298	AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREP	357				
Query 358	QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFL	417				
Sbjct 358	QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFL	417				
Query 418	YSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK	458				
Sbjct 418	YSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK	458				

110. The “Query” sequence represents SEQ ID NO:2 of Dix; the “S[u]bj[e]ct” sequence represents SEQ ID NO:2 of the '681 Patent; the sequence positioned in-between denotes amino acid residues that are common between the two aligned sequences. Other symbols are the same as previously discussed. As with the Papadopoulos '758 Patent (Ex. 1036), the two sequences differ from each other by six amino acid residues. In particular, SEQ ID NO:2 of Dix (i) lacks three amino acid residues, “SDT” (serine-aspartic acid-threonine), that are found in SEQ ID NO:2 of the '681 Patent; and (ii) contains three additional amino acid residues,

“GPG” (glycine-proline-glycine), that are not found in SEQ ID NO:2 of the ’681 Patent.

111. A POSA would, therefore, understand that Dix (Ex. 1037) discloses a VEGF Trap “R1R2” amino acid sequence that does not satisfy the recited sequence limitations of the ’681 Patent.

112. Daly, a published Regeneron patent application, also makes clear to a POSA that “R1R2” is a genus of VEGF Traps that encompasses proteins having VEGFR1 domain 2 and VEGFR2 domain 3 (Ex. 2087⁴⁸ at ¶¶ 5-6), including:

- Proteins having VEGFR domains directly fused or connected via a spacer region (*id.* at ¶ 6);
- Proteins having “at least one alteration, *e.g.*, a deletion, addition, and/or substitution” to one or more of the domains (*id.* at ¶ 30);
- Two full-length VEGF TrapR1R2 molecules having sequence alterations in the Fc region (*id.* at ¶¶ 23, 38-39, 48-49, 67); and
- Several Fc-truncated “R1R2” “mini-traps” (*id.* at ¶¶ 37-39, 63, 70-72, 77-79).

Hence, Dixon’s structural statements concerning “VEGF Trap-Eye” could encompass any one of the sequences reported by Daly.

113. The prior art also reported different molecular weights for “VEGF Trap-Eye.” For example, Ni reported in 2009 that “VEGF Trap-Eye ... is a 110-

⁴⁸ U.S. Patent Application Publication No. 2006/0058234 A1 (“Daly”).

kDa recombinant protein” (Ex. 2363⁴⁹ at 403), while a 2010 publication reports that “VEGF Trap-Eye (Regeneron Inc.) is a 115-kDa recombinant fusion protein” (Ex. 2088⁵⁰ at 49). Similar differences in molecular weights (note that 1 kDa is 1,000 Daltons (Da), *i.e.*, 1,000 g/mol) were reported for Regeneron’s VEGF-Traps generally. *See* Ex. 2089⁵¹ at 667 (“VEGF Trap, a 110 kDa soluble protein....”); Ex. 2090⁵² at 144 (“VEGF Trap is a 115 kDa recombinant fusion protein....”).

114. In contrast, the molecular weight of aflibercept was consistently reported as 115 kDa. *See, e.g.*, Ex. 2091⁵³ at 596 (“[A]flibercept is a soluble fusion protein.... Its molecular weight is 115 kDa....”); Ex. 2092⁵⁴ at [0010] (reporting a molecular weight “which is substantially less than that of the biologic drug Avastin [the recombinant humanized monoclonal antibody Bevacizumab] (115 kDa for aflibercept *versus* 160 kDa for Avastin)”).

⁴⁹ Ni et al., *Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration*, 223 OPTHALMOLOGICA 401 (2009) (“Ni”).

⁵⁰ Iacono et al., *Antivascular Endothelial Growth Factor in Diabetic Retinopathy*, 46 DEVS. OPTHALMOL. 39 (2010).

⁵¹ Stewart et al., *Predicted Biological Activity of Intravitreal VEGF Trap*, 92 BRIT. J. OPTHALMOL. 667 (2008).

⁵² Do et al., *An Exploratory Study of the Safety, Tolerability and Bioactivity of a Single Intravitreal Injection of Vascular Endothelial Growth Factor Trap-Eye in Patients with Diabetic Macular Oedema*, 93 BRIT. J. OPTHALMOL. 144 (2009).

⁵³ Moroney et al., *Aflibercept in Epithelial Ovarian Carcinoma*, 5 FUTURE ONCOL. 591 (2009).

⁵⁴ U.S. Patent Application Publication No. 2010/0160233 A1 to Bissery et al. published on June 24, 2010.

115. A POSA would recognize that reported differences in molecular weights among VEGF Trap-Eye proteins, as well as those between the reported molecular weights of VEGF Trap-Eye and aflibercept, point to differences in the amino acid sequence. Specifically, a 5,000-Da molecular weight difference corresponds to as many as some 42 amino acid residues (since the average molecular weight of a standard (*i.e.*, found in proteins) amino acid residue is about 110 Da). Ex. 2093⁵⁵ at 1271-72; Ex. 2094⁵⁶ at 11. A POSA would, therefore, understand that a 5,000-Da difference in the reported molecular weights of VEGF Trap-Eye could correspond to marked differences in the amino acid sequences of proteins called “VEGF Trap-Eye.” Consequently, these reported differences would suggest to a POSA that the term “VEGF Trap-Eye” referred to a family of fusion proteins with different amino acid sequences.

116. In any event, these differences in reported molecular weights, coupled with Dixon’s genus description of VEGF Trap-Eye as a soluble “fusion protein of binding domains of [human] VEGF receptors-1 and -2 attached to the Fc fragment of human IgG,” (Ex. 1006 at 1576), would support the conclusion that VEGF Trap-

⁵⁵ Hachiya et al., *Increase in Respiratory Cost at High Growth Temperature Is Attributed to High Protein Turnover Cost in Petunia x hybrida Petals*, 30 PLANT, CELL, & ENV’T 1269 (2007).

⁵⁶ Piques et al., *Ribosome and Transcript Copy Numbers, Polysome Occupancy and Enzyme Dynamics in Arabidopsis*, 5 MOLECULAR SYS. BIOL. 314 (2009).

Eye referred to a genus of protein sequences that may include, but not necessarily be limited to, the amino acid sequence of aflibercept.

117. As such, and contrary to the opinion offered by Dr. Chaum at ¶ 51 of his declaration (Ex. 1002), Adis’s listing of “aflibercept” with “VEGF Trap,” “VEGF Trap-Eye,” and “VEGF TRAP (R1R2),” would not suggest to a POSA that “VEGF Trap-Eye” corresponds to only “aflibercept,” but rather that “VEGF Trap-Eye,” like “VEGF Trap” and “VEGF TRAP (R1R2)” (or “VEGF TrapR1R2”), may include multiple amino acid sequences.

118. Petitioner’s reference to Regeneron’s 10-Q Securities and Exchange Commission (“SEC”) filing (Paper 2, 38-39 (citing Ex. 1057)) to equate VEGF Trap-Eye with aflibercept is also incorrect. Regeneron’s 2009 10-Q describes *aflibercept and VEGF Trap-Eye as separate and distinct products*. Specifically, Regeneron expressly stated in the 10-Q that it had three late-stage candidates—aflibercept was identified as one of those products and VEGF Trap-Eye as another. *See* Ex. 1057⁵⁷ at 18 (“Our late stage programs are aflibercept (VEGF Trap), which is being developed in oncology ... [and] VEGF Trap-Eye, which is being developed in eye diseases using intraocular delivery....”). In addition, the Clinical Programs section of Regeneron’s 10-Q has a subsection for “Aflibercept (VEGF Trap) – Oncology” and a different subsection for “VEGF Trap-Eye – Ophthalmologic Diseases.” *Id.* at

⁵⁷ Regeneron Pharms., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009).

18-20; *see also id.* at 25 (describing distinct clinical events and plans for aflibercept and for VEGF Trap-Eye); *id.* at 29 (setting forth different estimated costs for each of the projects); Ex. 2362 (Heier Retinal Physician 2009) at 2 (“VEGF Trap-Eye has been developed exclusively for ophthalmic use.”).

119. Indeed, Regeneron’s 10-Q SEC filing even cautioned against the use of “aflibercept” in ophthalmic indications, stating that “[w]hile we believe that aflibercept would not be well tolerated if administered directly to the eye, if aflibercept is ever approved for the treatment of certain cancers, there is a risk that third parties will attempt to repackage aflibercept for use and sale for the treatment of wet AMD and other diseases of the eye, which would present a potential low-cost competitive threat to the VEGF Trap-Eye if it is ever approved for sale.” Ex. 1057 at 55. Thus, contrary to Petitioner’s unwarranted assertion, a POSA actually would have good reasons to believe that aflibercept and VEGF Trap-Eye are separate and distinct products intended in the treatment of different medical indications.

4. None of Petitioner’s references discloses that VEGF Trap Eye corresponds to—and only to—the recited sequences

120. Petitioner and Dr. Chaum point to various Regeneron’s patents, published patent application, and journal publication—the ’173 Patent (Ex.

1013⁵⁸), '758 Patent (Ex. 1036⁵⁹), Dix's published patent application ("Dix"; Ex. 1037⁶⁰) and the two Regeneron publications "Gomez-Manzano" (Ex. 1011⁶¹) and "Rudge 2007" (Ex. 1014⁶²)—to contend that "'VEGF Trap-Eye,' 'VEGF TrapR1R2,' and 'aflibercept' referred interchangeably to the same molecule having the same amino acid and nucleic acid sequences." See Paper 2 (Petition) at 34-35; Ex. 1002 at ¶¶ 51-54, 123. I disagree.

121. None of the aforementioned patent references discloses an amino acid sequence identified as VEGF Trap-Eye (or aflibercept for that matter) and other VEGF Traps, including other VEGF-TrapR1R2 sequences, known in the prior art.

122. For example, Dr. Chaum relies on the '173 Patent's disclosure of SEQ ID NO:2 (see Ex. 1002 at ¶53 (citing Ex. 1013)) but ignores that the same patent discloses and incorporates by reference a number of other VEGF TrapR1R2 known amino acid sequences. See, e.g., Ex. 1013 at 4:50-58 ("In various embodiments, the VEGF trap is selected from the group consisting of ... Flt-1D2-Flk-1D3-FcΔC1(a),

⁵⁸ U.S. Patent No. 7,531,173 B2.

⁵⁹ U.S. Patent No. 7,374,758 B2.

⁶⁰ U.S. Patent Application Publication No. 2006/0217311 A1.

⁶¹ Gomez-Manzano et al., *VEGF Trap Induces Antiglioma Effect at Different Stages of Disease*, 10 NEURO-ONCOLOGY 940 (2008) ("Gomez-Manzano").

⁶² Rudge et al., *VEGF Trap Complex Formation Measures Production Rates of VEGF, Providing a Biomarker for Predicting Efficacious Angiogenic Blockade*, 104 PROC. NAT'L ACAD. SCI. USA 18363 (2007).

and VEGFR1R2-FcΔC1(a). For a more detailed description of these and other VEGF-receptor-based antagonists..., see PCT WO/00/75319, the contents of which are incorporated in their entirety herein by reference.”). I understand that WO/00/75319 (Ex. 2095⁶³) is the publication of International Application No. PCT/US00/14142, which is a priority document for the Papadopoulos ’758 Patent. The ’319 WO Publication discloses the same nucleic acid and amino acid sequences for Flt1D2.Flk1D3.FcΔC1(a) as in the Papadopoulos ’758 Patent in its Figures 21A-21C. Ex. 2095 at 21:16-17; pp. 132-34, Figs. 21A-21C. As discussed above in paragraphs 106-108, the amino acid sequence of Flt1D2.Flk1D3.FcΔC1(a) disclosed in the Papadopoulos ’758 Patent (and in the ’319 WO Publication) is not the same as that in the challenged claims of the ’681 Patent. The ’173 Patent does not identify any of its disclosed amino acid sequences as being that of VEGF Trap-Eye.

123. The Papadopoulos ’758 Patent (Ex. 1036) discloses many VEGF Trap amino acid and nucleic acid sequences but do not identify any of them as that for VEGF Trap-Eye (or aflibercept for that matter). Nor does the Papadopoulos ’758 Patent use the terms VEGF Trap-Eye or aflibercept. Moreover, the Papadopoulos ’758 Patent identifies more than a dozen of VEGF Trap amino acid and nucleic acid sequences, as well as multiple “VEGF Trap_{R1R2}” amino acid

⁶³ International Publication No. WO 00/75319 A1 (“the ’319 WO Publication”).

sequences, including SEQ ID NO:16 and SEQ ID NO:12. Papadopoulos calls both Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NO:12) and VEGFR1R2-FcΔC1(a) (SEQ ID NO:16) “R1R2.” Ex. 1036 at 10:4-6, 10:15-17, 26:13-21 (“These chimeric molecules [are] denoted R1R2 (Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a). . .”). Papadopoulos also extensively characterizes multiple R1R2 amino acid sequences. *See, e.g., id.* As discussed above, the VEGF Trap_{R1R2} of SEQ ID NO:12 disclosed in the Papadopoulos ’758 Patent does not satisfy the recited sequence limitations of the ’681 Patent. Simply put, the Papadopoulos ’758 Patent does not present any disclosed amino acid sequence as that of VEGF Trap-Eye and disclose multiple amino acid sequences that a POSA would understand as those of VEGF Trap and VEGF Trap_{R1R2}.

124. Dr. Chaum also points to disclosures related to SEQ ID NO:4 in Ex. 1037 (Dix) to purportedly disclose the recited VEGF antagonist sequence. *See* Ex. 1002 at ¶ 123 (citing Ex. 1037 at [0013]-[0014], [0030]). However, Dr. Chaum overlooks that Dix discloses multiple amino acid sequences (SEQ ID NO:2 and SEQ ID NO:4) and their corresponding nucleic acid sequences (SEQ ID NO:1 and NO:3), each in agreement with different VEGF Trap_{R1R2} amino acid and nucleic acid sequences. *See* Ex. 1037 at pp. 7-12. As discussed above, the VEGF Trap_{R1R2} of SEQ ID NO:2 disclosed in Dix does not satisfy the recited sequence limitations of

the '681 Patent. Dix thus does not correlate any disclosed amino acid sequence as being that of VEGF Trap-Eye.

125. None of Petitioner's cited patents or patent applications uses the terms aflibercept or VEGF Trap-Eye in connection with any of their disclosed sequences. Disclosure of the recited sequences among others known in the prior art does not teach a POSA that VEGF Trap-Eye would necessarily possess the amino acid or the nucleic acid sequence of the challenged claims of the '681 Patent. The mere *possibility* that VEGF Trap-Eye could include the recited amino acid or nucleic acid sequence does not establish that the sequence is *necessarily* present in a prior art reference.

126. Finally, contrary to Dr. Chaum's assertions (Ex. 1002 at ¶¶ 51-53), neither of the two Regeneron journal publications—whether Gomez-Manzano (Ex. 1011) or Rudge 2007 (Ex. 1014)—uses the terms aflibercept, VEGF Trap, or VEGF Trap-Eye in connection with any sequences. *See* paragraph 83 above.

127. In view of the foregoing, it is my opinion that *none* of petitioner's cited references discloses that VEGF Trap-Eye *necessarily* had the same amino acid sequence as aflibercept or the claimed amino acid sequence by January 13, 2011.

I hereby declare 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 are made with the knowledge that willful false statements and the like are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: October 6, 2023



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