UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Regeneron Pharmaceuticals, Inc., Plaintiff, vs. Merus B.V., Defendant.	Civil Action No. 14-CV-1650 [rel.14-CV-1651 (KBF)] **ECF Case** Hon. Katherine B. Forrest

DEFENDANT MERUS'S ANSWER AND FIRST AMENDED COUNTERCLAIMS

In response to Plaintiff Regeneron Pharmaceuticals, Inc.'s ("Regeneron") Complaint, Defendant Merus B.V. ("Merus") admits, denies, and avers as follows:

INTRODUCTION

1. Merus admits that Regeneron brought an action for infringement of Regeneron's alleged intellectual property. Merus admits that Merus is an innovative company in making and investigating therapeutic antibodies using its own proprietary technology. Merus otherwise denies the allegations set forth in paragraph 1.

2. The allegations contained in paragraph 2 are argument, to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 2.

3. Merus denies paragraph 3 as written, and Merus admits that it is an entity that has been invested in by Pfizer Venture Investments, a division of Pfizer Inc., and Johnson & Johnson Development Corporation, among other investors.

4. The allegations contained in paragraph 4 are argument, to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 4.

5. Merus admits that Regeneron is a corporation organized and existing under the laws of the State of New York, with its place of business at 777 Old Saw Mill River Road, Tarrytown, New York 10591. Merus is without information sufficient to form a belief as to the truth of the remaining allegations of paragraph 5. To the degree a response is required, Merus denies the allegations set forth in paragraph 5.

6. Admitted.

7. Admitted.

JURISDICTION AND VENUE

8. Merus denies Regeneron has any meritorious claim arising under the Patent Act, 35 U.S.C. § 100 *et seq*., including § 271. Merus admits that in this action Regeneron has alleged infringement under the Patent Act, 35 U.S.C. § 100 *et seq*., including § 271. The remaining allegations in paragraph 8 contain legal conclusions and do not require a response. To the degree a response is required, Merus denies the allegations set forth in paragraph 8.

9. The allegations contained in paragraph 9 are conclusions of law to which no response is required.

10. Merus admits that it has certain business dealings with Taconic Farms and Pfizer. The remaining allegations contained in paragraph 10 are conclusions of law to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 10.

11. Merus admits that it has an office and labs located in the Netherlands. Merus otherwise denies the allegations set forth in paragraph 11.

12. Merus admits that it has business dealings with certain U.S. companies, including Pfizer, Taconic Farms, Bay City Capital and Johnson & Johnson, and admits that certain of its employees attend and participate in conferences and trade shows in the United States raising awareness of its proprietary technology. Merus admits that it has registered trademarks with the United States Patent and Trademark Office ("USPTO"), and has filed patent applications with the USPTO. The remaining allegations in paragraph 12 contain legal conclusions and/or are too vague and do not require a response. To the degree a response is required, Merus denies the remaining allegations set forth in paragraph 12.

13. The allegations contained in paragraph 13 are conclusions of law to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 13.

INTRA-DISTRICT ASSIGNMENT

14. Merus is informed and believes that this Court has denied Regeneron's request to transfer this action to the White Plains Division and is informed and believes that this action will proceed before this Court in Manhattan. Except as expressly admitted, Merus denies the allegations set forth in paragraph 14.

BACKGROUND FACTS

15. Merus admits that antibodies are important biological molecules, and have various applications. Merus admits that United States Patent No. 8,502,018 (the "'018 Patent) is the subject of this action. The remaining allegations contained in paragraph 15 are argument, to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 15.

16. Merus is without information sufficient to form a belief as to the truth of the allegations of paragraph 16. To the degree a response is required, Merus denies the allegations set forth in paragraph 16.

17. Merus is without information sufficient to form a belief as to the truth of the allegations of paragraph 17. To the degree a response is required, Merus denies the allegations set forth in paragraph 17.

18. Merus admits that Pfizer Venture Investments and Johnson & Johnson, among others, have invested in Merus. The remaining allegations contained in paragraph 18 are argument, to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 18.

COUNT ONE

(Patent Infringement)

19. Merus incorporates by reference the answers set forth in paragraphs 1–18 as if fully set forth herein. Merus denies all allegations of infringement.

20. Merus admits that the '018 Patent is titled "Methods of modifying eukaryotic cells," and that the face of the patent states that the patent was issued on August 6, 2013. Merus denies that Drs. Andrew Murphy, George Yancopoulos, Margaret Karow, Lynn Macdonald, Sean Stevens, David Valenzuela, and Aris Economides were all named inventors at the time the patent issued, and that the '018 Patent was duly or legally issued, and deny any suggestion or implication that any claim of the '018 Patent is valid or enforceable. Merus otherwise denies the allegations set forth in paragraph 20.

21. Merus admits that Exhibit A to Regeneron's Complaint (D.I. 1) appears to be an incomplete copy of the '018 Patent. The remaining allegations in paragraph 21 contain legal

conclusions and do not require a response. To the degree a response is required, Merus denies the allegations set forth in paragraph 21.

22. Merus admits that the face of the '018 Patent states that the patent has 20 claims. Merus denies that paragraph 22 accurately recites the language of claim 9 of the '018 Patent, but admit that claim 9 recites the following language:

> 1. A genetically modified mouse, comprising in its germline human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus.
>
> * * *
>
> 9. The mouse of **claim 1,** wherein the mouse produces an antibody that comprises a human variable region and a mouse constant region.

23. Merus denies that paragraph 23 accurately recites the language of the '018 Patent, but admits that the '018 Patent recites the following language:

> A transgenic mouse is created that produces hybrid antibodies containing human variable regions and mouse constant regions. This is accomplished by a direct, in situ replacement of the mouse variable region genes with their human counterparts. The resultant hybrid immunoglobulin loci will undergo the natural process of rearrangements during B-cell development to produce the hybrid antibodies.
>
> Subsequently, fully-human antibodies are made by replacing the mouse constant regions with the desired human counterparts. This approach will give rise to therapeutic antibodies much more efficiently than previous methods, e.g. the "humanization" of mouse monoclonal antibodies or the generation of fully human antibodies in HUMAB™ mice. Further, this method will succeed in producing therapeutic antibodies for many antigens for which previous methods have failed. This mouse will create antibodies that are human variable region-mouse constant region, which will have the following benefits over the previously available HUMAB™ mice that produce totally human antibodies. Antibodies generated by the new mouse will retain murine Fc regions which will interact more efficiently with the other components of the mouse B cell receptor complex, including the signaling components required for appropriate B cell

> differentiation (such as Iga and Igb). Additionally, the murine Fc regions will be more specific than human Fc regions in their interactions with Fc receptors on mouse cells, complement molecules, etc. These interactions are important for a strong and specific immune response, for the proliferation and maturation of B cells, and for the affinity maturation of antibodies.

24. The allegations contained in paragraph 24 recite claim terms, and are therefore conclusions of law to which no response is required. To the degree a response is required, Merus denies the allegations set forth in paragraph 24.

25. Denied.

26. Merus admits that it is aware of the '018 Patent as of the filing of this Answer. Merus further admits that it is participating in a European Patent Office Opposition proceeding with respect to European Patent No. 1 360 287. Merus further admits that, on its face, European Patent No. 1 360 287 purports to claim priority to U.S. Patent Application No. 09/784,859. Merus admits that it has filed its own U.S. patent applications that describe and claim aspects of its own innovative technology and development work. Merus admits that some of these applications cite to patents or patent applications owned by Regeneron. Merus further admits that, on its face, U.S. Patent No. 6,596,541 purports to have issued from U.S. Patent Application No. 09/784,859. Merus further admits that, on its face, the "Related Application Data" for the '018 Patent states:

> (60) Continuation of application No. 13/154,976, filed on Jun. 7, 2011, which is a continuation of application No. 11/595,427, filed on Nov. 9, 2006, which is a continuation of application No. 10/624,044, filed on Jul. 21, 2003, now abandoned, which is a division of application No. 09/784,859, filed on Feb. 16, 2001, now Pat. No. 6,596,541, which is a continuation-in-part of application No. 09/732,234, filed on Dec. 7, 2000, now Pat. No. 6,586,251, application No. 13/164,176, which is a continuation of application No. 11/595,427, filed on Nov. 9, 2006.
>
> (60) Provisional application No. 60/244,665, filed on Oct. 31, 2000.

The allegation that "Merus cites U.S. Patent No. 6,596,541" lacks specificity, and is denied as written. Merus otherwise denies the allegations set forth in paragraph 26.

27. Denied.

28. Denied.

PRAYER FOR RELIEF

29. This section constitutes a request for relief to which no response is required. To the extent that this section may be deemed to allege any facts or legal entitlements to the relief requested, Merus denies all such allegations. Merus denies that Regeneron is entitled to any of the requested relief.

DEMAND FOR JURY TRIAL

30. Merus joins Regeneron's request for a jury trial on all issues triable by jury.

GENERAL DENIAL

31. Merus denies all allegations in Regeneron's Complaint not expressly admitted.

DEFENSES

32. Merus alleges and asserts the following defenses in response to the allegations in Regeneron's Complaint, undertaking the burden of proof only as to those defenses deemed affirmative defenses by law, regardless of how such defenses are denominated herein.

I. First Defense (Failure to State a Claim)

33. The allegations of Regeneron's Complaint fail to state a claim upon which relief can be granted and should be dismissed under Fed. R. Civ. P. 12(b)(6).

II. Second Defense (Non-Infringement)

34. Merus does not infringe (literally or under the doctrine of equivalents), and at all relevant times to this action has not infringed any valid and enforceable claim of the '018 Patent.

III. Third Defense (Invalidity)

35. The '018 Patent is invalid for failure to satisfy one or more of the conditions and requirements of patentability set forth in 35 U.S.C. §§ 101 *et seq.*, including, but not limited to, 35 U.S.C. §§ 101, 102, 103, 112, 116, and/or 282, or under the judicially created doctrines of invalidity or unenforceability.

IV. Fourth Defense (No Willful Infringement)

36. The Complaint fails to state a claim for willful infringement. Merus has not, and does not willfully infringe any valid and enforceable claim of the '018 Patent.

V. Fifth Defense (No Exceptional Case)

37. None of Merus's actions or lack of actions support any determination that this is an exceptional case under 35 U.S.C. § 285.

VI. Sixth Defense (Laches, Estoppel, Waiver, Acquiescence and Unclean Hands)

38. Regeneron's claims are barred by one or more of the doctrines of laches, estoppel, waiver, acquiescence, and unclean hands from enforcing, or claiming damages with respect to any claim of the '018 Patent.

VII. Seventh Defense (Prosecution Laches)

39. The '018 Patent is unenforceable due to the equitable defense of prosecution laches arising from Regeneron's unexplained and unreasonable delay in prosecuting the application that led to the issuance of the '018 Patent.

40. The "Related U.S. Application Data" for the '018 Patent is disclosed as follows:

> (60) Continuation of application No. 13/154,976, filed on Jun. 7, 2011, which is a continuation of application No. 11/595,427, filed on Nov. 9, 2006, which is a continuation of application No. 10/624,044, filed on Jul. 21, 2003, now abandoned, which is a division of application No. 09/784,859, filed on Feb. 16, 2001, now Pat. No. 6,596,541, which is a continuation-in-part of application No. 09/732,234, filed on Dec. 7, 2000, now Pat. No. 6,586,251, application No.

13/164,176, which is a continuation of application No. 11/595,427, filed on Nov. 9, 2006.

(60) Provisional application No. 60/244,665, filed on Oct. 31, 2000.

41. The '018 Patent issued on or about August 6, 2013, and purports to claims priority to a series of applications dating back to Provisional Application No. 60/244,665 (the "'665 Application"), filed October 31, 2000. Merus denies that '018 Patent is entitled to such priority.

42. More than twelve years lapsed since the '665 Application was filed and the '018 Patent issued. Regeneron unreasonably and inexplicably delayed in prosecuting the '018 Patent.

43. Merus is prejudiced by Regeneron's unreasonable delay because it has prevented timely resolution of Merus's rights. Merus continued its investment and development of the allegedly infringing technology during the pendency of the '018 Patent's prolonged prosecution.

VIII. Eight Defense (Doctrine of Equivalents and Prosecution History Estoppel)

44. Regeneron is barred from asserting any equivalents under the doctrine of equivalents and/or by the doctrine of prosecution history estoppel from asserting any scope of the '018 Patent that would cover Merus's MeMo mouse because of statements made during prosecution of the application that lead to the '018 Patent.

IX. Ninth Defense (35 U.S.C. § 271(e))

45. Regeneron's claims of infringement are barred in whole or in part by 35 U.S.C. § 271(e)(1).

46. Merus's allegedly infringing technology is reasonably related to the development and submission of information under a Federal Law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

X. Tenth Defense (Failure to Mark)

47. On information and belief, Regeneron did not comply with the marking and notice provisions of 35 U.S.C. § 287 and therefore has no claim for damages before filing suit.

XI. Eleventh Defense (No Injunctive Relief)

48. Regeneron is not entitled to injunctive relief because any injury to Regeneron is not immediate or irreparable, Regeneron has an adequate remedy at law, the public interest would be disserved by an injunction, and the balance of equities does not favor Regeneron.

XII. Reservation of Additional Defenses

49. Merus reserves the right to assert additional defenses in the event that discovery or other analysis indicates that additional defenses are appropriate.

COUNTERCLAIMS

Defendant Merus B.V. ("Merus") asserts the following counterclaims against Regeneron Pharmaceuticals Inc. ("Regeneron").

THE PARTIES

50. Merus is a corporation organized and existing under the laws of the Netherlands, with its principal place of business at Padualaan 8 (postvak 133), 3584 CH Utrech, The Netherlands.

51. Regeneron is a corporation organized and existing under the laws of the State of New York, with its principal place of business at 777 Old Saw Mill River Road, Tarrytown, New York 10591.

JURISDICTION AND VENUE

52. These counterclaims arise under the Declaratory Judgment Act and the Patent Statute of the United States of America, Titles 28 and 35 of the United States Code. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

53. This Court has personal jurisdiction over Regeneron because Regeneron has submitted itself to this Court's jurisdiction by filing its Complaint in this Court. Regeneron purports to be a New York corporation with a registered New York agent and, on information and belief, Regeneron has purposefully availed itself of the benefits and protections of this state.

54. Regeneron purports to be the owner of the entire right, title and interest in and to the '018 Patent.

55. Venue in this Court is proper based on the choice of forum by Regeneron and pursuant to 28 U.S.C. §§ 1391(b), (c) and/or 1400(b).

56. Regeneron has accused Merus of infringement of U.S. Patent No. 8,502,018 (the "'018 Patent"). Merus denies that any of its alleged products infringe any valid and enforceable claim of the '018 Patent.

57. Regeneron's filing of its Complaint, which includes allegations that Merus infringes the '018 Patent, has created an actual and justiciable controversy between Merus and Regeneron with respect to non-infringement, invalidity, and unenforceability of the '018 Patent.

THE PATENT-IN-SUIT

58. The "'018 Patent, on its face, is titled "Methods of modifying eukaryotic cells."

59. The '018 Patent, on its face, purports to have issued from U.S. Patent Application 13/164,176 filed June 20, 2011.

60. On information and belief, Regeneron claims to be the owner of the '018 Patent.

FIRST COUNTERCLAIM

(Declaration that Merus Does Not Infringe the '018 Patent)

61. Merus repeats and re-allege paragraphs 1–60 as if set forth specifically herein.

62. Merus is entitled to a declaratory judgment that Merus does not infringe, either directly or indirectly, and has not infringed, either directly or indirectly, any valid and enforceable claim of the '018 Patent.

SECOND COUNTERCLAIM

(Declaration of Invalidity of the '018 Patent)

63. Merus repeats and re-allege paragraphs 1–62 as if set forth specifically herein.

64. Merus is entitled to a declaratory judgment that the '018 Patent is invalid for failure to satisfy one or more of the requirements for patentability specified in 35 U.S.C. §§ 101 *et seq.*, including, but not limited to, 35 U.S.C. §§ 101, 102, 103, 112, 116, and/or 282, or under the judicially created doctrines of invalidity or unenforceability.

THIRD COUNTERCLAIM

(Declaration of Unenforceability of the '018 Patent)

65. Merus repeats and re-allege paragraphs 1–64 as if set forth specifically herein.

A. Persons Owing A Duty Of Candor To The Patent Office During Prosecution Of The '018 Patent

66. U.S. Patent Application No. 13/164,176 (the "'176 Application"), entitled "Method of Modifying Eukaryotic Cells" was filed on about June 20, 2011. The '176 application issued as the '018 Patent on August 6, 2013.

67. The '176 Application was assigned to primary examiner Magdalene K. Sgagias for examination.

68. The Application Data Sheet submitted with the '176 Application names Drs. Andrew J. Murphy and George D. Yancopoulos as inventors.

69. Inventors Murphy and Yancopoulos signed a "Declaration and Power of Attorney" in connection with the '176 Application on or about November 3, 2006. A copy of the '176 Declaration is attached hereto as Exhibit 1.

70. In signing the '176 Declaration, inventors Murphy and Yancopoulos each made the following acknowledgements:

> I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled "METHODS OF MODIFYING EUKARYOTIC CELLS", the specification of which is attached hereto.
>
> I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.
>
> I acknowledge the duty to disclose information of which I am aware that is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

(Ex. 1, '176 Declaration at 1.)

71. The '176 Declaration appointed Valeta Gregg and Dr. Ying-Zi Yang as "attorney and agent, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith and to file any International Applications that are based thereon under the provisions of the Patent Cooperation Treaty." (Ex. 1, '176 Declaration at 1–2.)

72. Attorney Dr. Tor E. Smeland, a Senior Patent Attorney at Regeneron, and current Assistant General Counsel worked with Gregg and Yang in preparing and/or prosecuting the '176 Application and/or was substantively involved in the preparation or prosecution of the '176 Application.

73. For example, attorney Smeland signed the June 2011 Utility Patent Application Transmittal form, a June 20, 2011 Application Data Sheet, a September 20, 2011 Information Disclosure Statement, a July 26, 2012 Terminal Disclaimer to Obviate a Provisional Double Patenting Rejection Over A Pending "Reference" Application, a July 26, 2012 Reply to Non-Final Office Action, a January 11, 2013 Reply to Final Office Action, and participated in an interview with Examiner Sgagias, the Examiner's Supervisor Peter Paras, and Quality Assurance Specialist Gerald Leffers on or about March 11, 2013.

74. On or about February 19, 2013, "A Revocation of Power of Attorney With a New Power of Attorney" was filed with the '176 Application. A copy of the February 2013 Revocation is attached hereto as Exhibit 2.

75. The February 2013 Revocation provided that:

> I hereby revoke all previous powers of attorney given in the above-identified application. I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application

> identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

(Ex. 2, February 2013 Revocation at 1.)

76. The February 2013 Revocation appointed practitioners at Customer Account Number 112969 as attorney(s) or agent(s) to prosecute the '176 Application and transact all business in the United States Patent and Trademark Office connected therewith. (*Id*.)

77. Upon information and belief, the practitioners at Customer Account Number 112969 identified in the February 2013 Revocation included at least attorney Brendan T. Jones.

78. A Change of Correspondence Address Application was filed by attorney Jones on or about March 25, 2013. A copy of the March 2013 Change of Correspondence is attached hereto as Exhibit 3.

79. The March 2013 Change of Correspondence stated that Jones was the attorney or agent of record. As noted above, Smeland continued to be substantively involved in the prosecution of the '176 Application, including participating in an Examiner interview, and being on correspondence related to the '176 Application both with the USPTO, and within Regeneron.

80. At least each of the foregoing individuals identified in paragraphs 66–79 above—namely attorneys Smeland and Jones—thus owed a duty of candor to the USPTO during prosecution of the '176 Application.

81. As set forth below, upon information and belief, at least one or more of the individuals identified in paragraphs 66–79, particularly attorneys Smeland and Jones, breached their duty of candor to the USPTO by failing to disclose material information with an intent to deceive the USPTO.

B. The Prosecution of the '176 Application

82. During the prosecution of the '176 Application, in the face of repeated novelty and obviousness rejections by the Examiner, the agents with a duty to disclose material information, including attorneys Smeland and Jones, repeatedly sought to distinguish the prior art before the Examiner on the basis that it did not teach insertion or integration of human variable region gene segments into the mouse immunoglobulin loci.

83. Upon information and belief, references that were material to patentability, which disclosed targeting at the mouse immunoglobulin loci were known at least attorneys Smeland and Jones, who had a duty to disclose such information to the USPTO, but were not disclosed during prosecution of the '176 Application.

84. On or about January 26, 2012 the USPTO mailed a Non-Final Office Action regarding '176 Application. A copy of the January 26, 2012 Office Action is attached hereto as Exhibit 4.

85. Among other rejections, the Office Action rejected claims 1–19 under 102(e) as being anticipated by U.S. Patent Application Publication 2006/0015957 ("Lonberg").

86. The January 26, 2012 Office Action, for example, contained the following opinion regarding the patentability of certain pending claims in the '176 Application:

> Lonberg and Kay teach heterologous unrearranged immunoglobulin human heavy and light chain transgenes useful for producing transgenic mice (paragraphs 24-26, 32, 225-248,251-252,260,268, and 279, also claims 1-10, 15-21,23, and 25) and transgenes are typically integrated into host chromosomal DNA, into germline DNA [0292].

(Ex. 4, January 26, 2012 Office Action, at 3).

87. The January 26, 2012 Office Action, for example, further contained the following opinion regarding patentability:

> Lonberg and Kay teach the production of chimeric human variable region/mouse constant region antibodies through trans-switching (Lonberg and Kay, paragraphs 108, 319), thus the mouse does not comprise a human immunoglobulin constant region gene.

(Ex. 4, January 26, 2012 Office Action, at 4).

88. On or about July 26, 2012 a Reply to the Non-Final Office Action was submitted to the Patent Office. A copy of the July 26, 2012 Reply to Non-Final Office Action is attached hereto as Exhibit 5.

89. The July 26, 2012 Reply distinguished Lonberg on the basis that trans-switching does not disclose inserting human unrearranged variable regions into endogenous mouse loci and thus did not teach a mouse comprising in its germline human unrearranged variable region gene segments inserted at a mouse immunoglobulin locus:

> Lonberg does not disclose a mouse comprising in its germline human unrearranged variable region gene segments ***inserted at*** a mouse immunoglobulin locus. Instead, Lonberg discloses transgenes that are apparently randomly inserted at (unknown) loci. Lonberg simply lacks description of the claimed chimeric locus of claim 1. Amended claim 11 and amended claim 20 also recite a chimeric endogenous locus, which is not disclosed in Lonberg. Thus, regardless of whether Lonberg disclosed chimeric human variable/mouse constant antibody proteins, Lonberg does not anticipate the claims because a disclosure of trans-switching does not disclose the claimed germline modified endogenous loci. Because Lonberg does not disclose endogenous mouse loci that are modified as claimed, Lonberg does not anticipate the pending claims. Accordingly, Applicants request withdrawal of the anticipation rejection based on Lonberg.

(Ex. 5, July 26, 2012 Reply to Non-Final Office Action, at 4) (emphasis added).

90. On or about October 11, 2012 the USPTO mailed a Final Office Action regarding '176 Application. A copy of the October 11, 2012 Final Office Action is attached hereto as Exhibit 6.

91. Among other rejections, the October 2012 Final Office Action stated that Claims 1–19 remain rejected as being anticipated by Lonberg.

92. For example, the October 2012 Action rejected the pending claims because:

> Lonberg teaches making transgenic mice by preparing vector containing the unrearranged sequences of the human immunoglobulin (hIg) comprising more than 4 human heavy chain V segment genes, and transgenes comprising multiple human light chain V segment genes loci. The vector introduced into mouse ES cells and transgenes are typically integrated into host chromosomal DNA, into germline DNA and rearranging the human immunoglobulin genes to produce

> chimeric human variable region/mouse constant region antibodies. Lonberg specifically teaches the human unrearranged variable region gene segments inserted at a mouse immunoglobulin locus by teaching that knockout mice bearing endogenous heavy chain alleles with are functionally disrupted in the J.sub.H region only frequently exhibit trans-switching, typically wherein a rearranged human variable region (VDJ) encoded by a transgene is expressed as a fusion protein linked to an endogenous murine constant region [0315]. Methods and strategies apparent to those of skill in the art for deletion of a substantial portion of the heavy chain constant region genes and/or D-region genes accomplished by sequential deletion by homologous recombination targeting vectors, especially of the "hit-and-run" type and the like [0315].

(Ex. 6, October 11, 2012 Final Office Action, at 5) (emphasis original).

93. Additionally, the October 2012 Final Office Action rejected the pending claims of the '176 Application because Lonberg disclosed chimeric antibodies with human VDJ regions and mouse constant regions:

> Lonberg teaches hybridomas are identified from a pool of hybridoma clones comprising: trans-switched hybridomas that express heterohybrid immunoglobulin chains consisting essentially of a human VDJ region and a murine constant region [0176].

(Ex. 6, October 11, 2012 Final Office Action, at 5–6) (emphasis original).

94. On or about January 11, 2013, a Reply to the Final Office Action was submitted to the Patent Office in response to the October 2012 Final Office Action. A copy of the January 11, 2013 Reply to the Final Office Action is attached hereto as Exhibit 7.

95. The January 2013 Reply again argued novelty of the draft claims of the '176 Application over Lonberg, because the reference did not teach inserting human unrearranged variable region gene segments at the endogenous mouse immunoglobulin loci:

> The Lonberg paragraphs cited by the Examiner merely disclose that human transgenes for making human antibodies were mentioned in the art. ***None of the cited paragraphs suggest or even hint at placing unrearranged human immunoglobulin gene segments at an endogenous mouse locus***, much less a functional endogenous mouse locus. The cited potions of Lonberg leave no doubt whatsoever that the Lonberg mouse construction instructions were to build a transgenic mouse that makes fully human antibodies from transgenes that are distant from endogenous mouse immunoglobulin loci; i.e., they are synthetic loci

> randomly inserted into the mouse genome at a locus distant from any functional mouse immunoglobulin locus. Indeed, as is described in detail elsewhere in Lonberg, the Lonberg transgenic mouse requires that endogenous mouse immunoglobulin loci (both heavy and light chain loci) must be rendered non-functional to as to allow the fully human immunoglobulin transgenes to make fully human antibodies. ***There is absolutely no hint or suggestion in Lonberg to employ a functional endogenous mouse locus having inserted unrearranged human immunoglobulin variable region gene segments in the functional locus***.

(Ex. 7, January 11, 2013 Reply to Final Office Action at 5–6).

96. While, the January 2013 Reply also contested that Lonberg did not disclose chimeric human/variable mouse constant antibodies (Ex. 7, January 11, 2013 Reply to Final Office Action at 5–6), it is noteworthy that the '176 Application itself expressly conceded that Lonberg does in fact suggest making such antibodies, leaving the only dispute before the USPTO as to novelty whether the prior art disclosed insertion into the mouse immunoglobulin locus. '018 Patent at 20:20-35 ("The use of chimeric antibodies, which utilize human variable regions with mouse constant regions through B cell maturation . . . has been suggested (U.S. Patent No. 5,770,429[1]).").

97. On or about February 1, 2013, the USPTO mailed an Office Action rejecting claims 1–19 as anticipated by Lonberg. A copy of the February 1, 2013 Office Action is attached hereto as Exhibit 8.

98. The February 2013 Office Action maintained, for example, that Lonberg taught insertion into a mouse immunoglobulin locus:

> Lonberg teaches a schematic representation of the human heavy chain minilocus transgenes pHC1 and pHC2, and the light chain minilocus transgenes pKC1, pKC1e, and the light chain minilocus transgene created ***by homologous***

---

[1] U.S. Patent Application Publication 2006/0015957 ("Lonberg") cited by the examiner says in the related application data that it is "a continuation-in-part of U.S. Ser. No. 08/728,463 filed Oct. 10, 1996, which is a continuation-in-part of ***U.S. Ser. No. 08/544,404*** filed 10 Oct. 1995…". (Emphasis added). U.S. Patent Application No. 08/544,404 was filed on or about October 10, 1995 and issued as U.S. Patent No. 5,770,429 on or about June 23, 1998.

> ***recombination*** between pKC2 and Co4 ***at the site indicated*** [0099] FIG. 56]. Therefore, as required in amended claim 1, Lonberg teaches germline human unrearranged variable region segments inserted at an endogenous mouse immunoglobulin locus…

(Ex. 8, February 1, 2013 Office Action at 3) (emphasis original).

99. Upon information and belief, on or about March 11, 2013, an Applicant-Initiated Interview was held before the Examiner Sgagias, Examiner's Supervisor Paras, and Quality Assurance Specialist Leffers. Applicant's attorney representatives Jones and Smeland discussed that Lonberg does not teach integration of human unrearranged immunoglobulin genes into an endogenous site of a mouse immunoglobulin locus as required by the instant claims. A copy of the Applicant-Initiated Interview Summary is attached hereto as Exhibit 9. The file history does not convey how or why the applicants received an interview with the Examiner's Supervisor.

100. On or about April 19, 2013, an Examiner-Initiated Interview was held between Examiner Sgagias and attorney Jones, where it was discussed that the instant Application is in the process of allowance. A copy of the Examiner-Initiated Interview Summary is attached hereto as Exhibit 10.

101. On or about April 26, 2013 the USPTO mailed a Notice of Allowance and Fee(s) due for the '176 Application. A copy of the Examiner's Statement of Reasons for Allowance was attached to the April 2013 Notice, and stated "[t]he prior art ***does not teach*** or suggest a genetically modified mouse comprising, in its germline cells, ***human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus***." A copy of the April 2013 Allowance and the Examiner's Statement of Reasons for Allowance are attached hereto as Exhibit 11.

102. On or about April 26, 2013 attorney Jones mailed an Interview Summary to the USPTO. The April 2013 Interview Summary stated, "[a]pplicant's representatives discussed that

Lonberg et al. does not disclose the integration of human unrearranged immunoglobulin variable region gene segments into a germline mouse immunoglobulin locus. In light of this discussion, it was agreed that the Examiner would reconsider the pending rejections." A copy of the April 2013 Interview Summary is attached hereto as Exhibit 12.

103. The Issue Fee for the '018 Patent was paid on or about June 28, 2013. A copy of the Issue Fee Transmittal is attached hereto as Exhibit 13.

104. As alleged previously, the '018 Patent issued on or about August 6, 2013. A copy of the Issue Notification is attached hereto an Exhibit 14.

C. Non-Disclosure of the Brüggemann & Neuberger (1996) Reference

Materiality of the Brüggemann & Neuberger (1996) Reference

105. On or about August 1996, Marianne Brüggemann and Michael S. Neuberger published an article entitled "Strategies for expressing human antibody repertoires in transgenic mice." A copy of the Brüggemann & Neuberger (1996) reference is attached hereto as Exhibit 15.

106. Regeneron asserts that the Asserted Claims of the '018 Patent have a conception date of no later than January 19, 2001 and are entitled to a priority date of no later than February 16, 2001, the filing date of parent application U.S. Serial No. 09/784,859. (Ex. 16, Regeneron's May 19, 2014 Disclosure of Asserted Claims and Infringement Contentions, at 6).

107. The Brüggemann & Neuberger (1996) reference was published prior to the earliest alleged priority date of the '176 Application. Based on its publication and priority dates, therefore, the Brüggemann & Neuberger (1996) reference would qualify as prior art to the Patents-in-Suit under at least 35 U.S.C. §§ 102(a), (b) and/or 103.

108. Among other things, the Brüggemann & Neuberger (1996) reference discloses a "transgenic mouse approach, mice carrying human V-gene segments in germline configuration rearrange and express these transgenes in their lymphoid tissue." (Ex. 15, at 391).

109. Specifically, Brüggemann & Neuberger (1996) recognized the benefits of genetically modified mice which have human V-gene segments integrated into the mouse immunoglobulin locus—the very issue at least attorneys Smeland and Jones argued, was an element that was not found in the Lonberg reference.

110. Brüggemann & Neuberger (1996) states:

> An attractive alternative would ***be to replace the mouse Ig loci with the human Ig loci; in this way it might be also possible to retain and exploit any possible regulatory sequences in the mouse loci that are located distal to protein coding regions***. . . . Animals have been generated in which the mouse Cκ exon and mouse Cγ1 gene have been replaced by equivalent human genes. Although this yields mice that produce repertoires of chimeric (as opposed to fully human) antibodies, it clearly constitutes a major step forward. Furthermore, technologies for directed gene replacement (e.g., using the Cre-loxP system) might allow the generation of animals in which much of the DNA of the mouse Ig loci is substituted by human Ig-gene DNA.

(Ex. 15, at 394–95) (emphasis added).

111. The Brüggemann & Neuberger (1996) reference therefore taught "replac[ing] the mouse Ig loci with the human Ig loci; in this way it might be also possible to retain and exploit any possible regulatory sequences in the mouse loci that are located distal to protein coding region" before January 2001.

112. Further demonstrating the materiality of the Brüggemann & Neuberger (1996) reference to the '018 Patent, the USPTO rejected related continuation applications—citing the Brüggemann & Neuberger (1996) reference—that claim related subject matter as the '018 Patent and rely on the same or substantially the same specification.

113. For example, U.S. Patent Application No. 13/719,819 (the "'819 Application"), entitled "Method of Modifying Eukaryotic Cells" was filed on or about December 19, 2012.

114. The Cross-Reference to Related Applications in '819 Application traces back to the '859 patent application, from which the '018 Patent issued:

> This application is a continuation of U.S. Serial No. 13/154,976, filed 07 June 2011, which is a continuation of U.S. Serial No. 11/595,427, filed 09 November 2006, which is a continuation of U.S. Ser. No. 10/624,044 filed 21 Jul. 2003, which is a divisional of U.S. Ser. No. 09/784,859, filed 16 Feb. 2001, now U.S. Pat. No. 6,596,541, which is a continuation-in-part of U.S. Set. No. 09/732,234, filed 7 Dec. 2000, now U.S. Pat. No. 6,585,251, which claims the benefit of U.S. Set. No. 60/244,665, filed 31 Oct. 2000, now abandoned (each application hereby incorporated by reference); this application is also a continuation of U.S. Serial No. 11/595,427, filed 09 November 2006, which is a continuation of U.S. Set. No. 10/624,044 filed 21 Jul. 2003, ***which is a divisional of U.S. Set. No. 09/784,859, filed 16 Feb. 2001***, now U.S. Pat. No. 6,596,541, which is a continuation-in-part of U.S. Ser. No. 09/732,234, filed 7 Dec. 2000, now U.S. Pat. No. 6,585,251, which claims the benefit of U.S. Ser. No. 60/244,665, filed 31 Oct. 2000, now abandoned (each application hereby incorporated by reference).

115. The "Field of the Invention" for the '819 Application, is identical to the '018 Patent, and is disclosed as follows:

> The field of this invention is a method for engineering and utilizing large DNA vectors to target, via homologous recombination, and modify, in any desirable fashion, endogenous genes and chromosomal loci in eukaryotic cells. The field also encompasses the use of these cells to generate organisms bearing the genetic modification, the organisms, themselves, and methods of use thereof.

116. Claim 1 of the '819 Application, for example, claims:

> A genetically modified mouse that expresses an antibody that comprises a human immunoglobulin sequence, wherein the human immunoglobulin sequence is derived from a human gene segment at a modified endogenous mouse immunoglobulin locus in the germline of the mouse.

117. The '819 Application was assigned to examiner Anoop Singh and thus had a different patent examiner than the '176 Application.

118. On or about October 23, 2013, the USPTO mailed an Office Action in the '819 Application. A copy of the October 23, 2013 Office Action is attached hereto as Exhibit 17.

119. The Examiner provisionally rejected the '819 Application, citing the Brüggemann & Neuberger (1996).

120. For example, the examiner noted:

> It is noted that the limitation of a method of producing antibody in the transgenic mouse of instant application would be obvious and known to one of ordinary skill in the art as evident from the teaching of Brüggemann who teaches a method of producing monoclonal antibody from transgenic mouse whose genome comprises human IgH transloci by challenging the transgenic mouse with an antigen and preparing a hybridoma expressing the antibody from said mouse (see table 2, page 396, col. 1, last para.). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to isolate hybridoma form the transgenic mouse disclosed in the instant application using the method of disclosed by Brüggemann that is implicit to the mouse expressing antibody .

(Ex. 17, '819 Application October 23, 2013 Office Action, at 23).

121. As the terms of the '018 Patent are apparently construed by Regeneron (*see, e.g.*, D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction, the Brüggemann & Neuberger (1996) reference alone or in combination with the referenced addressed herein, is accordingly "but for" material as the USPTO would not have allowed the claims of the '018 Patent had it been aware of the Brüggemann & Neuberger (1996).

Knowledge of the Brüggemann & Neuberger (1996) Reference During the Prosecution of the '018 Patent

122. Upon information and belief, at least attorneys Smeland and Jones were aware of the Brüggemann & Neuberger (1996) and its materiality during prosecution of the '176 Application.

123. For example, U.S. Patent Application U.S. Patent Application No. 11/809,473 (the "'473 Application"), entitled "Method of Modifying Eukaryotic Cells" was filed on about June 1, 2007.[2]

124. The '473 Application was initially assigned to examiner Joanne Hama and thus had a different patent examiner than the '018 Patent.

125. On or about May 13, 2009, the USPTO mailed a Non-Final Office Action. A copy of the May 2009 Office Action is attached hereto as Exhibit 18.

---

[2] The '473 Application stems from a different family as the '018 Patent.

126. Among other rejections, the USPTO rejected the '473 Application as unpatentable over Brüggemann & Neuberger (1996) in view of other references. For example, the May 2009 Office Action stated:

> ***Brüggemann et al., teach that an attractive alternative of the mice would be to replace the mouse Ig locus with the human Ig locus***; in this way, it might also be possible to retain and exploit any possible regulatory sequences in the mouse loci that are located distal to protein-coding regions.

(Ex. 18, '473 Application May 13, 2009 Non-Final Office Action at 6–7) (emphasis added).

127. On or about August 3, 2009 attorney Smeland responded to a Non-Final rejection of the '473 Application. A copy of the August 2009 Reply is attached hereto as Exhibit 19.

128. Attorney Smeland specifically discussed the teachings of Brüggemann & Neuberger in the August 3, 2009 Non-Final Office Action, stating (1996):

> Brüggemann, as the Examiner asserted, does not teach than an orthologous human coding sequence longer than 20 kb flanked by a mouse genomic sequence could be used in homologous recombination to replace the endogenous mouse sequence. Brüggemann acknowledges that differences between the mouse and human regulatory elements (i.e. promoters and enhancers) in their respective loci (e.g., Ig loci) remain unclear.

(Ex. 19, '473 Application August 3, 2009 Response to Non-Final Office Action at 5).

129. On or about November 4, 2009 the USPTO mailed a Final Rejection to the '473 Application, upholding the rejection as to Brüggemann & Neuberger (1996) in view of other art. A copy of the November 2009 Final Office Action is attached hereto as Exhibit 20.

130. The November 2009 Final Office action stated, for example:

> ***An artisan, given the teaching of Brüggemann et al., would have wanted to replace part of an entire region of a mouse Ig locus with human Ig sequence***, in order to make human or humanized antibodies.

(Ex. 20, '473 Application, November 11, 2009 Final Office Action at 8) (emphasis added).

131. On or around February 3, 2010 all pending claims of the '473 Application were canceled. A copy of the February 2010 amendment is attached hereto as Exhibit 21.

132. Thus, the very portion of the Brüggemann & Neuberger (1996) reference that was identified to attorney Smeland during prosecution of the '473 Application—and which he was unable to transverse—contradicted the arguments made by attorney Smeland concerning the Brüggemann & Neuberger (1996) reference while prosecuting the '176 Application.

133. Furthermore, on February 15, 2002 International Patent Application WO 02/066630 ("PCT '630 Application") entitled "Methods of Modifying Eukaryotic Cells" was filed under the Patent Cooperation Treaty. A copy of the PCT '630 Application is attached hereto as Exhibit 22.

134. The PCT '630 Application states "[t]his application claims priority to United States Patent Utility Application Serial No. 09/784,859, filed February 16, 2001, which is incorporated by reference herein." (Ex. 22,PCT '630 Application, at 1)

135. The "Field of the Invention" states, for example:

> The field of this invention is a method for engineering and utilizing large DNA vectors to target, via homologous recombination, and modify, in any desirable fashion, endogenous genes and chromosomal loci in eukaryotic cells. These large DNA targeting vectors for eukaryotic cells, termed LTVECs, are derived from fragments of cloned genomic DNA larger than those typically used by other approaches intended to perform homologous targeting in eukaryotic cells. The field of the invention further provides for a rapid and convenient method of detecting eukaryotic cells in which the LTVEC has correctly targeted and modified the desired endogenous gene(s) or chromosomal locus(loci). The field also encompasses the use of these cells to generate organisms bearing the genetic modification, the organisms, themselves, and methods of use thereof.

(Ex. 22, PCT '630 Application, at 1)

136. Claim 1 of the PCT '630 Application states, for example:

> 1. A method of replacing, in whole or in part, in a non-human eukaryotic cell an endogenous immunoglobulin variable region gene locus with an homologous or orthologous human gene locus comprising:
>
> > a) obtaining a large cloned genomic fragment containing, in whole or in part, the homologous or orthologous human gene locus

> b) using bacterial homologous recombination to genetically modify the cloned genomic fragment of (a) to create a large targeting vector for use in the eukaryotic cells (LTVEC);
>
> c) introducing the LTVEC of (b) into the eukaryotic cells to replace, in whole or in part the endogenous immunoglobulin variable gene locus; and
>
> d) using a quantitative assay to detect modification of allele (MOA) in the eukaryotic cells of (c) to identify those eukaryotic cells in which the endogenous immunoglobulin variable region gene locus has been replaced, in whole or in part, with the homologous or orthologous human gene locus

(Ex. 22, PCT '630 Application at 54).

137. The PCT '630 Application entered the National Stage at the European Patent Office, and was assigned European Patent Application No. 02709544.7 (the "EP '544 Application").

138. On or about April 2, 2012, a Third Party Observation ("TPO") was filed during the prosecution of the EP '544 Application. A copy of the TPO is attached hereto as Exhibit 23.

139. The TPO directed the European Examiner to the Brüggemann & Neuberger (1996) reference, specifically pointing out that Brüggemann & Neuberger (1996):

> ***discloses the concept of precisely replacing mouse Ig gene loci sequence with orthologous human Ig loci sequences in a way that preserves the regulatory sequences in the mouse loci'*** and 'the applicant is not the first to provide the concept of chimeric human/mouse immunoglobulin loci provided by manipulating the genome of mouse ES cells using direct in situ replacement with human orthologous in a way that preserves mouse endogenous control elements. This cannot form the basis of novelty or inventive step.'

(Ex. 23, April 2012 Third Party Observation in EP '544 Application, at 2–3) (emphasis added).

140. Upon information and belief, on or about April 3, 2012, Smeland became aware of the TPO, including the Brüggemann & Neuberger (1996) reference. (Ex. 24, Regeneron's Response to Court Interrogatory No. 1).

141. The EP '544 Application issued as European Patent No. 1 360 287 (the "EP 287 Patent) on or about September 9, 2012.

142. Further, on or about June 2013, Merus B.V., and Kymab Ltd. (and later joined by another company), filed Oppositions against EP '287 Patent citing numerous prior art references not disclosed during the '018 Patent prosecution. The Merus and Kymab Notices of Opposition are attached hereto as Exhibits 25 & 26.

143. The Brüggemann & Neuberger (1996) reference is among the references asserted in the June 2013 European Opposition. (Ex. 26, Kymab Notice of Opposition, at O1.)

144. Upon information and belief, Smeland was aware of the Brüggemann & Neuberger (1996) reference shortly after the Opposition to the EP '287 was filed. (Ex. 24, Regeneron's Response to Court Interrogatory No. 1).

145. Furthermore, U.S. Patent Application U.S. Patent Application No. 13/154,976 (the "'976 Application"), entitled "Method of Modifying Eukaryotic Cells" was filed on about June 2, 2011.

146. The Cross-Reference to Related Applications in the '976 Application states:

> This application is a continuation of U.S. Serial No. 11/595,427, filed 09 November 2006, which is a continuation of U.S. Ser. No. 10/624,044 filed 21 Jul. 2003, which is a divisional of U.S. Ser. No. 09/784,859, filed 16 Feb. 2001, now U.S. Pat. No. 6,596,541, which is a continuation-in-part of U.S. Ser. No. 09/732,234, filed 7 Dec. 2000, now U.S. Pat. No. 6,585,251, which claims the benefit of U.S. Ser. No. 60/244,665, filed 31 Oct. 2000, now abandoned, each of which is incorporated by reference herein.

147. The "Field of the Invention" for the '976 Application, for example, is disclosed as follows:

> The field of this invention is a method for engineering and utilizing large DNA vectors to target, via homologous recombination, and modify, in any desirable fashion, endogenous genes and chromosomal loci in eukaryotic cells. The field also encompasses the use of these cells to generate organisms bearing the genetic modification, the organisms, themselves, and methods of use thereof.

148. The '976 Application, for example, claims:

1. A genetically modified mouse, comprising in its germline

> (a) a hybrid human variable/mouse constant immunoglobulin heavy chain locus comprising a replacement of mouse immunoglobulin heavy chain V, D, and J gene segments with human heavy chain immunoglobulin V, D, and J gene segments, wherein the replacement is at a mouse immunoglobulin heavy chain locus, and wherein the human V, D, and J gene segments are linked to an endogenous mouse immunoglobulin heavy chain constant region gene sequence;
>
> (b) a hybrid human variable/mouse constant immunoglobulin light chain locus comprising a replacement of mouse immunoglobulin light chain V and J gene segments with human light chain immunoglobulin V and J gene segments, wherein the replacement is at a mouse immunoglobulin light chain locus, and wherein the human V and J gene segments are linked to an endogenous mouse immunoglobulin light chain constant region gene sequence;
>
> (c) a functional murine immunoglobulin heavy chain intronic enhancer (Em) at an endogenous murine immunoglobulin heavy chain locus, wherein the Em is functionally able to participate in recombination of the human heavy chain V, D, and J gene segments; and,
>
> (d) a functional murine immuloglobulin heavy chain 3' enhancer region at an endogenous murine immunoglobulin heavy chain locus, wherein the functional murine immunoglobulin heavy chain 3' enhancer regions is functionally able to participate in one or more of class switching and heavy chain gene expression during B cell differentiation;
>
> wherein the mouse expresses a chimeric human variable/mouse constant antibody, and the mouse is incapable of forming a chimeric human variable/mouse constant antibody gene by *trans*-splicing or *trans*-rearrangements.

149. On or about March 21, 2013, a "Power of Attorney to Prosecute Application Before the USPTO" was entered in the '976 Application, and appointed practitioners at Customer Account Number 112969 as attorney(s) or agent(s) to prosecute the '976 Application. A copy of the March 2013 Power of Attorney to Prosecute Applications Before the USPTO is attached as Exhibit 27.

150. Upon information and belief, the practitioners at Customer Account Number 112969 identified in the Power of Attorney to Prosecute Applications Before the USPTO included at least attorney Jones.

151. On or about April 2013 a Third Party Submission citing Brüggemann & Neuberger (1996) was filed in connection with the '976 Application. A copy of the Third Party Submission is attached hereto as Exhibit 28.

152. On or about April 30, 2013, the USPTO mailed a Notice that a Third-Party Submission was filed and entered into the '976 Application file history. A copy of the April 2013 Notice is attached hereto as Exhibit 29.

153. On or about July 26, 2013, attorney Jones submitted a Preliminary Amendment canceling all the pending claims in the '976 Application.

154. Upon information and belief, the PTO has not issued an Office Action regarding the '976 Application.

155. Upon information and belief, a PTO examiner has not been assigned to review the '976 Application.

156. Attorney Jones was aware of the Brüggemann & Neuberger (1996), at least upon receipt of that Third Party Submission. (Ex. 24, Regeneron Interrogatory Response to Court Interrogatory No. 1).

157. Upon information and belief, at least one or more attorneys Smeland and Jones would have recognized that the Brüggemann & Neuberger (1996) reference was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are apparently construed by Regeneron (*see*, D.I. 95, D.I. 96-1) and/or under their broadest reasonable construction.

158. Indeed, upon receipt of the Non-Final Office Action in the '473 Application, on or about May 13, 2009, at least attorney Smeland would have recognized that the Brüggemann & Neuberger (1996) reference was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction. During that Application, the Examiner identified the very section in which Brüggemann & Neuberger (1996) informs an artisan "***to replace part of an entire region of a mouse Ig locus with human Ig sequence***," in order to make human or humanized antibodies. This concerns the very element Smeland alleged to have been missing from the prior art during the '018 Patent prosecution, leading to the Examiner allowing the claims.

159. Upon information and belief, and upon receiving the Third Party Submission in the '976 application, on or about April 30, 2013, attorney Jones canceled the pending claims of the '976 Application because he knew the Brüggemann & Neuberger (1996) reference was material to patentability as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

160. Upon receipt of the TPO during prosecution of the the EP '544 Application, on or about April 3, 2012, at least attorney Smeland would have recognized the Brüggemann & Neuberger (1996) reference was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction. Indeed, during that Third Party Submission, again, the relevance of Brüggemann & Neuberger (1996), and its disclosure of integrating human immunoglobulin DNA into the mouse immunoglobulin locus was highlighted.

161. Upon receipt of the European Opposition to the EP '287 Patent, on or about June 12, 2013, at least attorney Smeland would have recognized the Brüggemann & Neuberger (1996) reference was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

162. Upon receipt of the Third Party Submission in the '976 Application, on or about April 30, 2013, at least attorney Jones would have recognized the Brüggemann & Neuberger (1996) reference was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

Failure to Disclose the Brüggemann & Neuberger (1996) Reference With The Intent to Deceive

163. Despite having knowledge of the Brüggemann & Neuberger (1996) reference and its materiality, at least one or more of attorneys Smeland and Jones did not disclose the existence of the Brüggemann & Neuberger (1996) reference to the USPTO during prosecution of the '018 Patent.

164. Upon information and belief, at least one or more of attorneys Smeland and Jones, failed to disclose the Brüggemann & Neuberger (1996) reference with intent to deceive the USPTO.

165. Upon information and belief, on or about November 25, 2013 (*i.e.*, a few weeks after the issue date of the '018 Patent) attorney Jones submitted and an information disclosure statement ("IDS"), in the '819 Application. The November 2013 IDS; (1) identified the Brüggemann & Neuberger (1996) reference; (2) requested that the USPTO consider the reference during the prosecution of this Application; and (3) that the references be made of

record therein and appear among the "References Cited" on any patent to issue therefrom. A copy of the November 2013 IDS is attached hereto as Exhibit 30.

166. Likewise, upon information and belief, attorney Jones submitted IDSs listing the Brüggemann & Neuberger (1996) in, at least, related U.S. Patent Applications Nos. 13/719842, 14/035,432, 14/036514, 14/036,518, 14/036,530, 14/036,774, 14/036,778, 14/036,784, 14/036,865, 14/036,892, 14/046,279, 14/046,291, 14/080,114 after the issuance of the '018 Patent.

167. Indeed, in view of the disclosure of the Brüggemann & Neuberger (1996) reference to the USPTO in related patent applications, but the omission of the Brüggemann & Neuberger (1996) during prosecution of the '018 Patent, the single most reasonable inference to be drawn from attorneys Smeland's and Jones's failure to disclose the Brüggemann & Neuberger (1996) reference is an intent to deceive the USPTO.

168. Regeneron could have submitted an Information Disclosure Statement at least as early as the filing date of the '176 Application, and certainly prior to the issue date, so the examiner could have examined the claims in light of the Bruggemann & Neuberger (1996) reference.

169. The failure of at least one or more of attorneys Smeland and Jones to disclose the Brüggemann & Neuberger (1996) reference to the USPTO, particularly when (1) they argued to the Examiner during the '018 Patent prosecution that the prior art failed to disclose the targeting at the mouse immunoglobulin locus, and (2) that is what Brüggemann & Neuberger (1996) discloses, and (3) that reference had previously been brought to the attention of attorneys Smeland and Jones, combined with (4) their intent to deceive the USPTO, renders the '018 Patent unenforceable.

D. Nondisclosure of WIPO Patent Application No. WO 91/00906

Materiality of WIPO Patent Application No. WO 91/00906

170. On or about January 24, 1991 the World Intellectual Property Organization ("WIPO") published Patent Application No. WO 91/00906 (the "'906 Publication) entitled "Chimeric and Transgenic Animals Capable of Producing Human Antibodies." A copy of the '906 Publication is attached hereto as Exhibit 31.

171. The '906 Publication was published prior to the earliest effective filing date of the '176 Application. Based on its publication and priority dates, therefore, the '906 Publication would qualify as prior art to the Patents-in-Suit under at least 35 U.S.C. §§ 102(a), (b), and/or 103.

172. Among other things, the '906 Publication teaches, "a non-human eukaryotic animal having incorporated into its germline unrearranged DNA fragments bearing exogenous immunoglobulin (Ig) heavy chain gene segments." (Ex. 31, '906 Publication, at 5)

173. Further, the '906 Publication discloses, for example:

> Another aspect of this invention is an unrearranged DNA fragment for use in producing the animal of the invention. This DNA fragment is composed of at least the following elements: at least one exogenous variable Ig gene segment, at least one exogenous D Ig gene segment, at least one exogenous J Ig gene segment, and at least one μ heavy chain constant Ig region. The μ constant region is of exogenous or endogenous species origin, and is required to mediate allelic exclusion in the animal of this invention.
>
> * * *

(Ex. 31, the '906 Publication, at 6),

> the animals of this invention are designed by the integration into their germlines of DNA carrying unrearranged or only partially rearranged exogenous Ig gene segments.
>
> * * *

(Ex. 31, the '906 Publication, at 15),

> Transgenic animals can be produced by several standard procedures…. introduced Ig genes are expressed almost exclusively in the same tissues in which the homologous endogenous genes are expressed . . . . Alternatively, a naturally unrearranged human DNA fragment, as described above, can be introduced into isolated embryonal stem cells of the animal to create chimeric animals.

(Ex. 31, the '906 Publication, at 18–19).

174. The '906 Publication taught that "a naturally unrearranged human DNA fragment, as described above, can be introduced into isolated embryonal stem cells of the animal to create chimeric animals" before January 2001.

175. Further, the USPTO rejected related continuation applications—citing the '906 Publication—that claim related subject matter to the '018 Patent and rely on the same or substantially the same specification.

176. For example, U.S. Patent Application U.S. Patent Application No. 14/046,291 (the "'219 Application"), entitled "Method of Modifying Eukaryotic Cells" was filed on about October 2, 2013.

177. The Cross-Reference to Related Applications in '291 Application states:

> This application is a continuation of U.S. Pat. App. No. 13/719,842, filed December 19, 2012 and U.S. Pat. App. No. 13/719,819, filed on December 19, 2012, both of which are continuations of U.S. Pat. App. No. 13/154,976, filed June 7, 2011, which is a continuation of U.S. Pat. App. No. 11/595,427, filed November 9, 2006, which is a continuation of U.S. Pat. App. No. 10/624,044, filed July 21, 2003, now abandoned, which is a divisional of U.S. Pat. App. No. 09/784,859, filed February 16, 2001, now U.S. Pat. No. 6,596,541; each of which is incorporated by reference herein.

178. The "Field of the Invention" for the '291 Application, for example, is disclosed as follows:

> The field of this invention is a method for engineering and utilizing large DNA vectors to target, via homologous recombination, and modify, in any desirable fashion, endogenous genes and chromosomal loci in eukaryotic cells. The field also encompasses the use of these cells to generate organisms bearing the genetic modification, the organisms, themselves, and methods of use thereof.

179. Claim 1 of the '291 Application, for example, claims:

> 1. A mouse that expresses a human variable region immunoglobulin sequence that is expressed by a rearranged immunoglobulin locus that is derived from a germline immunoglobulin locus that comprises unrearranged human

> immunoglobulin variable domain segments and a mouse immunoglobulin constant domain sequence.

180. On or about January 22, 2014 the USPTO mailed a Non-Final Office Action, rejecting the pending claims in light of the '906 Publication:

> With respect to claim 1-3, 5-8, 10-12, 14-16 and 18, Wood et al [the '906 Publication] teach a mouse that expresses a human variable region immunoglobulin, wherein said mouse incorporated into its germline unrearranged DNA fragments bearing human immunoglobulin gene segments and a murine constant region said animal capable of rearranging said segments (see claims 5-8, 11 and 24, page 13 and 15, para. 3, page 20, line 17, page 22 line 18-20 and page 24, line 17-18, 24). Wood et al further teaches that the two unrearranged DNA fragments bearing the human heavy chain genes and the human light chain gene, respectively, may be injected into the same animal. It is further disclosed that the unrearranged DNA fragment of the invention may also contain appropriate transcriptional enhancer and promoter elements. Immediately upstream of the coding regions of the human Igs, the animal contains murine, constant region "switch" regions proximal to each constant region meeting the limitation of the claims.

181. As the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction, the '906 Publication alone or in combination with the referenced addressed herein, is accordingly "but for" material as the USPTO would not have allowed the claims of the '018 Patent had it been aware of the '906 Publication.

Knowledge of the '906 Publication Patent During the Prosecution of the '018 Patent

182. Upon information and belief, at least attorney Smeland was aware of the '906 Publication and its materiality during prosecution of the '018 Patent.

183. The '906 Publication is among the references asserted in the June 2013 European Opposition. (Ex. 26, Kymab's Notice of Opposition, at D8.)

184. Upon information and belief, on or about June 12, 2013, attorney Smeland was aware of the '906 Publication reference shortly after the Opposition to the EP '287 was filed. (Ex. 24, Regeneron's Response to Court Interrogatory No. 1).

185. Upon information and belief, at least attorney Smeland would have recognized that the '906 Publication was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

186. As alleged previously, the '018 Patent did not issue until August 6, 2013.

Failure to Disclose the '906 Publication During the Prosecution of the '018 Patent With the Intent to Deceive

187. Despite having knowledge of the '906 Publication reference and its materiality since at least on or about June 12, 2013, attorney Smeland did not disclose the existence of the '906 Publication to the USPTO during prosecution of the '018 Patent.

188. Upon information and belief, at least attorney Smeland failed to disclose the '906 Publication reference with intent to deceive the USPTO.

189. Indeed, the single most reasonable inference to be drawn from attorney Smeland's failure to disclose the '906 Publication is an intent to deceive the USPTO.

190. Regeneron could have submitted an Information Disclosure Statement at least as early as receiving knowledge of the European Opposition on or about June 12, 2013, and certainly prior to the issue date, so the examiner could have examined the claims in light of '906 Publication.

191. The failure of at least attorney Smeland to disclose the '906 Publication to the USPTO, combined with his intent to deceive the USPTO, renders the '018 Patent unenforceable.

E. Nondisclosure of Taki et al., (1993)

Materiality of the Taki et al., (1993) Reference

192. On or about November 19, 1993, Shinsuke Taki, Myriarn Meiering and Klaus Rajewsky published an article entitled "Targeted Insertion of a Variable Region Gene into

Immunoglobulin Heavy Chain Locus." A copy of the Taki et al., (1993) reference is attached hereto as Exhibit 32.

193. The Taki et al., (1993) reference was published prior to the earliest effective filing date of the '176 Application. Based on its publication and priority dates, therefore, the Taki et al., (1993) reference would qualify as prior art to the '018 Patent under at least 35 U.S.C. §§ 102(a), (b), and/or 103.

194. Among other things, the Taki et al., (1993) reference discloses a:

> mutant mouse strain has been generated in which a rearranged immunoglobulin heavy (H) chain variable (V) region gene is placed into the heavy chain locus in its natural position, replacing the J_H elements…The proper location of the transgene relative to the constant genes allows it to participate in isotype switching and undergo somatic hypermutation.

(Ex. 32, Taki et al., (1993), at Abstract).

195. Furthermore, Fig. 1 of Taki et al., (1993), for example, shows:

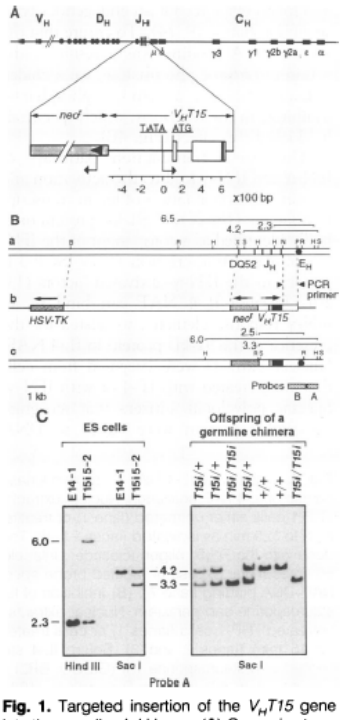

Fig. 1. Targeted insertion of the *V_HT15* gene into the germline IgH locus. (**A**) Genomic struc-

(Ex. 32, Taki et al., (1993), at Fig. 1).

196. Furthermore, Taki et al., (1993) describes, for example:

> a method of generating 'second generation' Ig transgenic mice, in which the transgene behaves like a normal rearranged Ig gene in terms of B cell-specific expression, class switching, and somatic hypermutation. The method is not only applicable to any rearranged V_H gene, but can be easily extended to light chain genes as well. Transgenic mice of this kind, generated by gene targeting, should provide useful mouse models for the in vivo analysis of antigen-specific B cell activation and tolerance, including models of allergic and autoimmune diseases.

(Ex. 32, Taki et al., (1993), at 1270).

197. Taki et al., (1993) taught, "mutant mouse strain [] generated in which a rearranged immunoglobulin heavy (H) chain variable (V) region gene is placed into the heavy chain locus in its natural position…" before January 2001.

198. Further, the USPTO rejected related continuation applications—citing the Taki et al., (1993) reference—that claim related subject matter to the '018 Patent and rely on the same or substantially the same specification.

199. For example, on or about October 23, 2013, the USPTO mailed an office action in the '819 Application rejecting the pending claims as obvious over Taki et al., (1993) in combination with other references.

200. For example, the examiner noted:

> Taki et al teaches mouse strain could be generated in which a rearranged immunoglobulin heavy (H) chain variable (V) region gene is placed into the heavy chain locus in its natural position, replacing the JH elements. Further, the proper location of the trans gene relative to the constant region genes allows it to participate in isotype switching and undergo somatic hypermutation (abstract). Taki et al further teaches a targeting vector to introduce a rearranged VH region gene into a chromosomal position where rearranged VH genes locate, 5' to the heavy chain enhancer to produce mouse ES cell (Taki, S. pages 1268, col. land Fig. I)
>
> * * *
>
> Therefore, it would have been *prima facie* obvious for a person of ordinary skill to combine the teachings of Lonberg, Sen and Tak[i] to characterize the transgenic mouse of Lonberg whose genome comprises a transgenic IgH locus

> comprising human IgH variable region (VH) DNA, and constant (C) region encoding DNA of a mouse, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention.

(Ex. 17, '819 Application, October 23, 2013 Office Action, at 15).

201. As the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction, the Taki et al., (1993) reference alone or in combination with the referenced addressed herein, is accordingly "but for" material as the USPTO would not have allowed the claims of the '018 Patent had it been aware of the Taki et al., (1993) reference.

Knowledge of Taki et al., (1993) During the Prosecution of the '018 Patent With The Intent to Deceive

202. Upon information and belief, at least attorneys Smeland and Jones would have recognized that the Taki et al., (1993) reference was material to patentability of the claims in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

203. The Taki et al., (1993) reference is among the references asserted in the June 2013 European Opposition. (Ex. 26, Kymab's Notice of Opposition, at D7).

204. Upon information and belief, at least attorney Smeland was aware of the Taki et al., (1993) reference shortly after the Opposition to the EP '287 was filed. (Ex. 24, Regeneron's Response to Court Interrogatory No. 1).

205. The Taki et al., (1993) reference is among the references disclosed in the Third Party Submission submitted in the '976 Application.

206. Attorney Jones was aware of the Taki et al., (1993), on or about April 30, 2013, upon receipt of that Third Party Submission '976 Application (Ex. 24, Regeneron's Interrogatory Response to Court Interrogatory No. 1).

207. Upon information and belief, at least attorneys Smeland and Jones would have recognized that the Taki et al., (1993) reference was material to patentability to the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

208. Upon receipt of the Third Party Submission in the '976 Application, on or about April 30, 2013, at least attorney Jones would have recognized that the Taki et al., (1993) reference was material to patentability to the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

209. Upon information and belief, and upon receiving the Third Party Submission in the '976 application, on or about April 30, 2013, attorney Jones canceled the pending claims of the '976 Application because he knew the Taki et al., (1993) reference was material to patentability.

210. Upon receipt of the European Opposition to the EP '287 Patent, on or about June 12, 2013, at least attorney Smeland would have recognized that the Taki et al., (1993) reference was material to patentability to the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

211. As alleged previously, the '018 Patent did not issue until August 6, 2013.

Failure to Disclose Taki et al., (1993) During the Prosecution of the '018 Patent With the Intent to Deceive

212. Despite having knowledge of the Taki et al., (1993) reference and its materiality, at least one or more of attorneys Smeland and Jones did not disclose the existence of the Taki et al., (1993) reference to the USPTO during prosecution of the '018 Patent.

213. Upon information and belief, on or about November 25, 2013 (*i.e.*, a few weeks after the issue date of the '018 patent) attorney Jones submitted an information disclosure statement ("IDS"), in the '819 Application. The November 2013 IDS; (1) listed the Taki et al., (1993) reference; (2) requested that the USPTO consider the reference during the prosecution of this Application; and (3) that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom. A copy of the November 2013 IDS is attached hereto as Exhibit 30.

214. Further, attorney Jones submitted IDSs listing the Taki et al., (1993) reference in, at least, related U.S. Patent Applications Nos. 13/719842, 14/035,432, 14/036514, 14/036,518, 14/036,530, 14/036,774, 14/036,778, 14/036,784, 14/036,865, 14/036,892, 14/046,279, 14/046,291, 14/080,114 after the issuance of the '018 Patent.

215. Regeneron could have submitted an Information Disclosure Statement at least as early as early as April 30, 2013, and certainly prior to the issue date, so the examiner could have examined the claims of the '176 Application in light of the Taki et al., (1993) reference.

216. Indeed, in view of the disclosure of the Taki et al., (1993) reference to the USPTO in related patent applications, but the omission of the Taki et al., (1993) during prosecution of the '018 Patent, the single most reasonable inference to be drawn from attorneys Smeland's and Jones's failure to disclose the Taki et al., (1993) reference is an intent to deceive the USPTO.

217. The failure of at least one or more of attorneys Smeland and Jones, to disclose the Taki et al., (1993) reference to the USPTO, combined with their intent to deceive the USPTO, renders the '018 Patent unenforceable.

F. Nondisclosure of Zou et al., (1994)

Materiality of the Zou et al., (1994) Reference

218. On or about 1994, Yong-Rui Zou, Werner Mueller, Hua Gu and Klaus Rajewsky published "Cre-loxP-mediated gene replacement: a mouse strain producing humanized antibodies." A copy of Zou et al., (1994) is attached hereto as Exhibit 33.

219. The Zou et al., (1994) reference was published prior to the earliest effective filing date of the '176 Application. Based on its publication and priority dates, therefore, the Zou et al., (1994) reference would qualify as prior art to the Patents-in-Suit under at least 35 U.S.C. §§ 102(a), (b), and/or 103.

220. Among other things, Zou et al., (1994) discloses:

> In these mutants, the entire Cγ1 gene is replaced by its human counterpart, except for the exons encoding the transmembrane and cytoplasmic portions of the γ1 chain; we hoped in this way to minimize the danger of disturbing membrane expression and signaling of the humanized IgG1 in the mouse.

(Ex. 33, Zou et al., (1994), at 1100).

221. The Zou et al., (1994) reference therefore taught "replac[ing] by [a] human counterpart, except for the exons encoding the transmembrane and cytoplasmic portions of the γ1 chain; . . . to minimize the danger of disturbing membrane expression and signaling of the humanized IgG1 in the mouse" before January 2001.

222. As the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction, the Zou et al., (1994) reference is accordingly "but for" material alone or in combination with the referenced addressed herein, as the USPTO would not have allowed the claims of the '018 Patent had it been aware of the Zou et al., (1994) reference.

Knowledge of the Zou et al., (1994) Reference Patent During the Prosecution of the '018 Patent

223. Upon information and belief, attorneys Smeland and Jones were aware of Zou et al., (1994) and its materiality during prosecution of the '018 Patent, as the terms of the '018 Patent

are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

224. The Zou et al., (1994) reference is among the reference disclosed in the TPO submitted in the EP '544 Application.

225. Upon receipt of the TPO during prosecution of the the EP '544 Application, on or about April 3, 2012, at least attorney Smeland would have recognized the Zou et al., (1994) reference was material to patentability of the draft claims prosecuted in the '018 Patent.

226. Upon information and belief, and upon receiving the Third Party Submission in the '976 application, on or about April 30, 2013, attorney Jones canceled the pending claims of the '976 Application because he knew the Zou et al., (1994) reference was material to patentability, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

227. The Zou et al., (1994) reference is among the reference disclosed in the TPO submitted in the '976 Application.

228. Upon information and belief, attorney Jones was aware of the Zou et al., (1994), upon receipt of that Third Party Submission '976 Application, on or about April 30, 2013.

229. The Zou et al., (1994) reference is among the references asserted in the June 2013 European Opposition. (Ex. 25, Merus's Notice of Opposition, at O2), and at least attorney Smeland would have recognized the Zou et al., (1994) reference was material to patentability of the draft claims prosecuted in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

230. Upon information and belief, on or about June 12, 2013, attorney Smeland was aware of the Zou et al., (1994) reference shortly after the Opposition to the EP '287. (Ex. 24,

Regeneron's Response to Court Interrogatory No. 1), and at least attorney Smeland would have recognized the Zou et al., (1994) reference was material to patentability of the draft claims prosecuted in the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

231. Upon information and belief, at least attorneys Smeland and Jones would have recognized that the Zou et al., (1994) reference was material to patentability of the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

232. As alleged previously, the '018 Patent did not issue until August 6, 2013.

Failure to Disclose the Zou et al., (1994) Reference During the Prosecution of the '018 Patent With the Intent to Deceive

233. Despite having knowledge of the Zou et al., (1994) reference and its materiality at least attorneys Smeland and Jones did not disclose the existence of the Zou et al., (1994) reference to the USPTO during prosecution of the '018 Patent.

234. Upon information and belief, at least attorneys Smeland and Jones failed to disclose the Zou et al., (1994) reference with intent to deceive the USPTO.

235. Indeed, the single most reasonable inference to be drawn from failure to disclose the Zou et al., (1994) is intent to deceive the USPTO.

236. Upon information and belief, on or about November 25, 2013 (*i.e.*, a few weeks after the issue date of the '018 patent) attorney Jones submitted and an information disclosure statement ("IDS"), in the '819 Application. The November 2013 IDS; (1) identified the Zou et al., (1994) reference; (2) requested that the USPTO consider the reference during the prosecution of this Application; and (3) that the references be made of record therein and appear among the

"References Cited" on any patent to issue therefrom. A copy of the November 2013 IDS is attached hereto as Exhibit 30.

237. Likewise, upon information and belief, attorney Jones submitted IDSs listing the Zou et al., (1994), at least, related U.S. Patent Applications Nos. 13/719842, 14/035,432, 14/036514, 14/036,518, 14/036,530, 14/036,774, 14/036,778, 14/036,784, 14/036,865, 14/036,892, 14/046,279, 14/046,291, 14/080,114 after the issuance of the '018 Patent.

238. Regeneron could have submitted an Information Disclosure Statement at least as early as early as April 2012, and certainly prior to the issue date, so the examiner could have examined the claims of the '176 Application in light of the Zou et al., (1994) reference.

239. Indeed, in view of the disclosure of the Zou et al., (1994) reference to the USPTO in related patent applications, but the omission of the Zou et al., (1994) during prosecution of the '018 Patent, the single most reasonable inference to be drawn from attorneys Smeland's and Jones's failure to disclose the Zou et al., (1994) reference is an intent to deceive the USPTO.

240. The failure of at least attorneys Smeland and Jones, to disclose the Zou et al., (1994) reference to the PTO, combined with their intent to deceive the USPTO, renders the '018 Patent unenforceable.

G. Prosecuting Anticipated Claims

Materiality of the '598 Patent

241. On or about June 5, 1995 inventors Raju Kucherlapati et al., filed U.S. Patent Application No. 08/464,582 (the "'582 Application") entitled "Generation of Xenogenic Antibodies."

242. The '582 Application issued as U.S. Patent No. 6,114,598 (the "'598 Patent") on or about September 5, 2000. A copy of '598 Patent is attached hereto as Exhibit 34.

243. Based on its publication and priority dates, therefore, the '598 Patent would qualify as prior art to the Patents-in-Suit under at least 35 U.S.C. §§ 102(e) and/or 103.

244. Among other things, the '598 Patent teaches, for example:

> The subject invention provides non-human mammalian hosts characterized by inactivated endogenous Ig loci and functional human Ig loci for response to an immunogen to produce human antibodies or analogs thereof. The hosts are produced by multiple genetic modifications of embryonic cells in conjunction with breeding. Different strategies are employed for recombination of the human loci randomly or at analogous host loci. Chimeric and transgenic mammals, particularly mice, are provided, having stably integrated large, xenogeneic DNA segments. The segments are introduced by fusion with yeast spheroplasts comprising yeast artificial chromosomes (YACs) which include the xenogeneic DNA segments and a selective marker such as HPRT, and embryonic stem cells.

(Ex. 34, at '598 Patent, at Abstract)

245. Furthermore, the specification of '598 Patent discloses, for example,

> In a second, alternative strategy, ***at least portions of the human heavy and light chain immunoglobulin loci are used to directly replace the corresponding endogenous immunoglobulin loci by homologous recombination*** in embryonic stem cells…

(Ex. 34, '598 Patent, at Col. 6:30–34) (emphasis added),

* * *

> In the second, alternative strategy described above, the number of steps may be reduced by providing at least a fragment of the human immunoglobulin locus within the construct used for homologous recombination with the analogous endogenous immunoglobulin, so that the human locus is substituted for at least a part of the host immunoglobulin locus, with resulting inactivation of the host immunoglobulin subunit locus.

(Ex. 34, '598 Patent, at Col. 8:37–49),

* * *

> For example, by isolating the variable region of the human IgH locus (including V, D, and J sequences), or portion thereof, and flanking the human locus with sequences from the murine locus, preferably sequences separated by at least about 5 kbp, in the host locus, preferably at least about 10 kbp in the host locus, one ***may insert the human fragment into this region in a recombinational event(s), substituting the human immunoglobulin locus for the endogenous variable region of the host immunoglobulin locus***.

(Ex. 34, '598 Patent, at Col. 10:55–64) (emphasis added).

246. Fig. 16C of the '598 Patent, reproduced below, is a diagram of a YAC vector containing human variable gene segments:

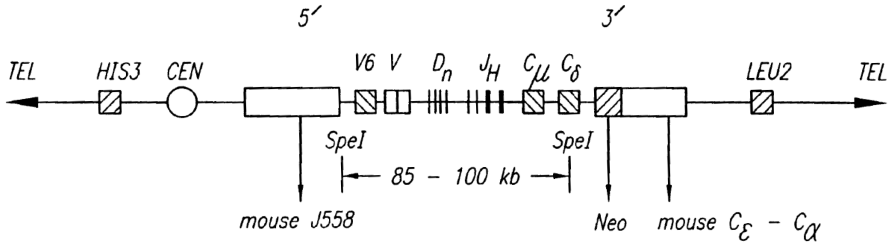

FIG. 16C

247. The '598 Patent therefore taught "substituting the human immunoglobulin locus for the endogenous variable region of the host immunoglobulin locus" before January 2001.

248. As the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction, the '598 Patent alone or in combination with the referenced addressed herein, is accordingly "but for" material as the USPTO would not have allowed at least claims 1–10 of the '018 Patent had it been aware of the '598 Patent.

249. On or about September 20, 2011, attorney Smeland filed an IDS during prosecution of the '176 Application. The IDS listed the '598 Patent as a reference for the examiner to consider. (Ex. 35, '176 Application IDS).

250. Upon information and belief, attorney Smeland understood or should have understood, upon submitting that September 2011 IDS, that the '598 Patent rendered at least claims 1-10 of the '018 Patent anticipated.

251. Upon information and belief, attorney Jones, upon making an appearance during the prosecution of the '018 Patent, understood or should have understood that the '598 Patent rendered at least claims 1-10 of the '018 Patent anticipated.

Prosecuted Claims Applicants Knew or Should Have Known Were Invalid

252. As originally filed on or about June 20, 2011, claim 1, for example, read as follows:

> 1. A genetically modified mouse, comprising in its germline human unrearranged variable region gene segments inserted at a mouse immunoglobulin locus.

(D.I. 1 at Exhibit A).

253. Despite his knowledge of the '598 Patent, attorney Smeland filed claim 1 knowing that the claim was anticipated by the '598 Patent.

254. Moreover, as originally filed on or about June 20, 2011, claim 11, for example, read as follows:

> 11. A genetically modified mouse, comprising in its germline human unrearranged variable region gene segments linked to a mouse constant region gene, ***wherein the mouse lacks a human constant region gene***.

(D.I. 1 at Exhibit A).

255. The specification to the '018 Patent does not support a limitation that the mouse lacks a human constant region gene. No place in the '018 patent's specification discloses producing a genetically modified mouse lacking a human constant gene, or the goal of excluding a human constant gene. (*See* D.I. 1 at Exhibit A).

256. Upon information and belief, attorney Smeland drafted claim 11 to include the limitation "wherein the mouse lacks a human constant region gene" because he understood that claim 1 was anticipated in light of the '598 Patent.

257. Furthermore, during the European Opposition, on or about January 28, 2014, Regeneron distinguished the '598 Patent on the basis that it does not disclose a functional endogenous immunoglobulin coding sequence:

> [T]here is no disclosure in column 10, lines 50-64 of [the '598 Patent] that the substitution it describes results in the ***operable linkage*** of human variable regions with endogenous constant regions. Rather, the human variable regions are to be operably linked to human constant regions when introduced into the host, consistent with the aim of producing fully human antibodies.

(Ex. 36, Regeneron's January 28, 2014 Response to the EP '287, at 18–21) (emphasis added).

258. Originally filed claims 1–10 of the '018 Patent, however, do not require "operable linkage." Therefore, by Applicants own admission claims 1–10 are anticipated by the the '598 Patent.

259. Indeed, upon information and belief, Regeneron submitted numerous auxiliary claims in the EP '287 Opposition, adding the term "operably linked" to try and distinguish the claims of the EP '287 Patent from the '598 Patent.

260. Despite attorneys Smeland's and Jones's knowledge that the '598 Patent anticipated at least claim 1 of the '018 Patent, they continued to prosecute claim 1.

261. Attorneys Smeland's and Jones's prosecution of claims 1–10—knowing that such claims were anticipated constituting affirmative egregious misconduct.

262. Attorneys Smeland's and Jones's affirmative egregious misconduct renders the claims of the '018 Patent unenforceable.

H. Failure to Disclosure Statements and Arguments Raised in the European Opposition Prior to the Issuance of the '018 Patent

Materiality of the Statements and Arguments from the EP '287 Opposition

263. On or about June 12, 2013, Opponents Merus and Kymab filed a Notice of Opposition to the EP '287 Patent, identifying various patent and publications that render the EP '287 Patent

invalid. A copy of Merus's and Kymab's Notices of Opposition are attached hereto as Exhibits Exhibits 25 & 26.

264. The Notice of Opposition identified, among others, the '598 Patent, Brüggemann & Neuberger (1996) references, the '906 Publication, the Taki et al., (1993) reference, and the Zou et al., (1994) reference. (*See e.g.*, Ex. 25, Merus's Notice of Opposition; Ex. 26, Kymab's Notice of Opposition).

265. On or about June 12, 2013, Opponents Merus and Kymab submitted a Statements of Facts and Arguments in support of its Opposition to the EP '287 Patent. A copy of the Statements of Facts and Arguments is attached hereto as Exhibits 37 & 38.

266. The Statements of Facts and Arguments describes many of the references identified in the Notice of Opposition and states how the various patent and publications alone, or in combination with other references, render the EP '287 Patent invalid.

267. For example, the Statements of Facts and Arguments describes the '598 Patent as follows:

> [The '598 Patent] describes in its Abstract that it discloses non-human mammalian hosts with inactivated endogenous Ig loci and function human Ig loci. :"Chimeric and transgenic mammals. Particularly mice, are provided, having stably integrated, large xenogenic DNA segments. 'Also at column 1, line 47 to 53 it is made clear that the issues addressed in the document relate to the problems of introducing large DNA fragments, intact, into mammalian cells, the efficiency of integration into the genome and the functionality and transmissibility of the introduced genes.'
>
> * * *
>
> **Column 3, line 50** discloses that host animals 'may have an entire endogenous immunoglobulin locus substituted by a portion of, or an entire, xenogeneic immunoglobulin locus.'
>
> * * *
>
> **Column 3, line 60:** discloses that 'novel methods are provided for introducing large segments of xenogeneic DNA of at least 100 kb, particularly human DNA,

> into host animals, particularly mice, by introducing a yeast artificial chromosome (YAC) containing a xenogeneic DNA segment of at least 100 kb into an embryonic stem cell for integration into the genome of the stem cell.'
>
> * * *
>
> **Column 6, line 30-36** discloses that: 'at least portions of the human heavy and light chain immunoglobulin loci are used to directly replace the corresponding endogenous immunoglobulin loci by homologous recombination in embryonic stem cells.'

(Ex. 38, Kymab's Statements of Facts and Arguments, at 19)

268. The Statements of Facts and Arguments further identifies how the '598 Patent, alone or in combination with other patents and publications, renders the claims of the EP '287 Patent invalid. (*See e.g.*, Ex. 38, Kymab's Statements of Facts and Arguments, at 24–37).

269. The Statements of Facts and Arguments, further describes, for example, the Brüggemann & Neuberger (1996) reference as follows:

> [Brüggemann & Neuberger (1996); referred to as D2] describes YACs of up to 1Mb (p392, column 2, line 39) and their use in cloning several V, J and C genes into YACs (p393, Figure 1). D2 indicates a desire to replace a mouse Ig locus with human Ig locus retaining regulatory sequences and that this has been done for some constant genes. It suggests that technologies using Cre-loxP could be used to generate animals in which "much of the DNA of the mouse Ig loci is substituted by human Ig-gene DNA". (D2, p394 last three words of page and first three lines p395)
>
> [Brüggemann & Neuberger (1996)] further discloses the concept of precisely replacing mouse Ig gene loci sequences with orthologous human Ig loci sequences in a way that preserves regulatory sequences in the mouse loci. Technology for such directed gene replacement (ie, direct "in situ" replacement) was known…

(Ex. 38, Kymab's Statements of Facts and Arguments, at 20–21).

270. The Statements of Facts and Arguments further identifies how Brüggemann & Neuberger (1996), alone or in combination with other patents and publications, renders the claims of the EP '287 Patent invalid. (*See, e.g.*, Ex. 38, Kymab's Statements of Facts and Arguments, at 27–30, 32–33).

271. The Statements of Facts and Arguments, also describes, for example, the '906 Publication as follows:

> [The '906 Publication] discloses chimeric transgenic non-human eukaryotes having incorporated into their germ line un-rearranged DNA fragments bearing exogenous immunoglobulin gene segments. Example 2 at p32 describes a construct comprising "an unrearranged human VH gene segment_ the human JH locus with a single upstream, unrearranged D segment, the murine mu gene including its upstream, unrearranged D segment, the murine mu gene including its upstream mu switch region, the murine gamma 2b switch region and the human gamma 1 coding region". Example 3 at page 35 describes the generation of transgenic mice from the construct described in Example 2.

(Ex. 38, Kymab's Statements of Facts and Arguments, at 23).

272. The Statements of Facts and Arguments further identifies how the '906 Publication, alone or in combination with other patents and publications, renders the claims of the EP '287 Patent invalid. (*See e.g.*, Ex. 38, Kymab's Statements of Facts and Arguments, at 25, 32).

273. The Statements of Facts and Arguments, also describes, for example, the Taki et al., (1993) reference as follows:

> [Taki et al., (1993)] describes precisely inserting (rearranged) exogenous variable region DNA upstream of endogenous mouse C region in a mouse IgH locus (p1268, Fig. 1) - here the inserted DNA is mouse. Targeted insertion is used, which involves" homologous recombination" (p1268, Fig 1 (B)) between incoming vector DNA and endogenous mouse IgH locus DNA There is disclosure that this "proper insertion" allows participation in isotype switching and somatic hypermutation ie, endogenous control is maintained (See Abstract).

(Ex. 38, Kymab's Statements of Facts and Arguments, at 23).

274. The Statements of Facts and Arguments, also describes, for example, the Zou et al., (1994) reference as follows:

> Zou relates to gene replacement using site specific recombinases, specifically producing humanized antibodies. It discloses producing chimeric loci by *in situ* replacement of target endogenous gene segments (p1099, Figure 1), described as a generally-applicable technique for inserting human lg DNA into a mouse IgH locus. Specifically [Zou et al., (1994)] teaches (see e.g. conclusion section) replacement of a mouse antibody heavy chain C region gene with its human

> counterpart (p1100 Fig 2). As such chimeric antibodies are made with human constant regions rather than mouse constant regions.

(Ex. 38, Kymab's Statements of Facts and Arguments, at 23).

275. The Statements of Facts and Arguments further identifies how the Zou et al., (1994) reference, alone or in combination with other patents and publications, renders the claims of the EP '287 Patent invalid. (*See e.g.*, Ex. 38, Kymab's Statements of Facts and Arguments, at 20–21, 28–32, 35).

276. Further demonstrating the materiality of the Statements of Facts and Arguments to the '018 Patent, the USPTO rejected related continuation applications that claim related subject matter as the '018 Patent and rely on the same or substantially the same specification—citing at least the Brüggemann & Neuberger (1996) reference, the '906 Publication, or the Taki et al., (1993) reference—and adopted similar arguments to those raised by Merus and Kymab in the EP '287 Opposition.

277. As the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction, the Statements of Facts and Arguments are accordingly "but for" material as the USPTO would not have allowed the claims of the '018 Patent had it been aware of the Statements of Facts and Arguments.

Knowledge of the Statements and Arguments from the EP '287 Opposition

278. Upon information and belief, on or about June 12, 2013, attorney Smeland was aware of the Statements of Facts and Arguments filed by Merus and Kymab in the EP '287 Opposition. (Ex. 24, Regeneron's Response to Court Interrogatory No. 1).

279. Upon information and belief, attorney Smeland would have known that the '598 Patent anticipates at least claims 1-10 of the '018 Patent.

280. Upon information and belief, attorney Smeland therefore would have known that the Statements of Facts and Arguments regarding the '598 Patent reference were material to patentability of the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

281. Upon information and belief, attorney Smeland would have known that Brüggemann & Neuberger (1996) informs "to replace the mouse Ig loci with the human Ig loci; in this way it might be also possible to retain and exploit any possible regulatory sequences in the mouse loci that are located distal to protein coding regions."

282. Upon information and belief, attorney Smeland therefore would have known that the Statements of Facts and Arguments regarding the Brüggemann & Neuberger (1996) reference were material to patentability of the claims of the '018 Patent , as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

283. Upon information and belief, upon receipt of the Statements of Facts and Arguments, at least attorney Smeland would have known that the Statements of Facts and Arguments regarding the '906 Publication discloses "a naturally unrearranged human DNA fragment, as described above, can be introduced into isolated embryonal stem cells of the animal to create chimeric animals."

284. Upon information and belief, attorney Smeland therefore would have known that the Statements of Facts and Arguments regarding the '906 Publication were material to patentability of the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

285. Upon information and belief, at least attorney Smeland would have known that the Statements of Facts and Arguments regarding the Taki et al., (1993) reference discloses "mutant mouse strain [] generated in which a rearranged immunoglobulin heavy (H) chain variable (V) region gene is placed into the heavy chain locus in its natural position…".

286. Upon information and belief, attorney Smeland therefore would have known that the Statements of Facts and Arguments regarding the Taki et al., (1993) reference were material to patentability of the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

287. Upon information and belief, at least attorney Smeland would have known that the Statements of Facts and Arguments regarding the Zou et al., (1994) reference discloses "replac[ing] by [a] human counterpart, except for the exons encoding the transmembrane and cytoplasmic portions of the γ1 chain; . . . to minimize the danger of disturbing membrane expression and signaling of the humanized IgG1 in the mouse."

288. Upon information and belief, attorney Smeland therefore would have known that the Statements of Facts and Arguments regarding the Zou et al., (1994) reference were material to patentability of the claims of the '018 Patent, as the terms of the '018 Patent are construed by Regeneron (*see, e.g.,* D.I. 95; D.I. 96-1) and/or under their broadest reasonable construction.

Failure to Disclose the Statements and Arguments from the EP '287 Opposition

289. Despite having knowledge of Statements of Facts and Arguments and its materiality, at least attorney Smeland did not disclose the existence of the Statements of Facts and Arguments to the USPTO during prosecution of the '018 Patent.

290. Upon information and belief, at least attorney Smeland failed to disclose the Statements of Facts and Arguments with intent to deceive the USPTO.

291. Indeed, the single most reasonable inference to be drawn from failure to disclose the Statements of Facts and Arguments is intent to deceive the USPTO.

292. The failure of at least attorney Smeland to disclose the Statements of Facts and Arguments to the USPTO, combined with his intent to deceive the USPTO, renders the '018 Patent unenforceable.

DEMAND FOR JURY TRIAL

293. Merus requests a jury trial on all issues triable by jury.

PRAYER FOR RELIEF

Wherefore Merus requests the following relief:

(i) That all claims against Merus be dismissed with prejudice and that all relief requested by Regeneron be denied;

(ii) That a judgment be entered declaring that Merus has not infringed and does not infringe, whether directly or indirectly, literally or by equivalents, any valid claim of the '018 Patent;

(iii) That a judgment be entered declaring that the claims of the '018 Patent are invalid;

(iv) That a judgment be entered declaring that the claims of the '018 Patent are unenforceable due to inequitable conduct;

(v) That, in the event that any claim of the '018 Patent is found valid, enforceable and infringed, Regeneron's damages claims are precluded, in whole or in part, by reason of laches, estoppel, prosecution laches, waiver, acquiescence, unclean hands or failure to mark;

(vi) That Regeneron be preliminary and permanently enjoined from threatening or initiating infringement litigation against Merus concerning the '018 Patent;

(vii) That judgment be entered finding and declaring that this case is exceptional under 35 U.S.C. § 285, and accordingly that Merus is entitled to recover reasonable attorneys' fees and costs upon prevailing in this action; and

(viii) That Merus be awarded such other relief as this Court deems just and equitable, or which the Court deems just and proper.

Dated: New York, NY
August 18, 2014

Kirkland & Ellis LLP

/s/ Patricia Carson

Patricia Carson
Peter B. Silverman
James H. McConnell
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, New York 10022
Telephone: (212) 446-4800
Facsimile: (212) 446-4900
patricia.carson@kirkland.com
peter.silverman@kirkland.com
james.mcconnell@kirkland.com

Attorneys for Merus B.V.