IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

REPLIGEN CORPORATION and THE REGENTS OF THE UNIVERSITY OF MICHIGAN, Plaintiffs, v. BRISTOL-MYERS SQUIBB COMPANY, Defendant.	Case No. 2:06-CV-004-TJW JURY TRIAL DEMANDED

AMENDED COMPLAINT

For their Amended Complaint plaintiffs Repligen Corporation ("Repligen") and The Regents of the University of Michigan ("University of Michigan") (collectively "Plaintiffs"), by and through the undersigned attorneys, allege as follows:

THE PARTIES

1. Plaintiff Repligen is a corporation organized under the laws of the state of Delaware, with its principal place of business at 41 Seyon Street, Building #1, Suite 100, Waltham, MA 02453.

2. Plaintiff University of Michigan is a constitutional corporation of the state of Michigan located in Ann Arbor, Michigan.

3. On information and belief, defendant Bristol-Myers Squibb Company ("Bristol-Myers") is a corporation organized under the laws of the state of Delaware, with its principal place of business at 345 Park Avenue, New York, NY 10154-0037.

JURISDICTION AND VENUE

4. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 1, *et seq*.

5. Subject matter jurisdiction is proper in this Court under 28 U.S.C. §§ 1331 and 1338.

6. This Court has personal jurisdiction over Bristol-Myers because, among other things, BMS regularly does business in this judicial district and further has appeared and answered the original complaint in this case.

7. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c) and 1400(b).

THE PATENT-IN-SUIT

8. United States Patent No. 6,685,941 ("the '941 patent"), entitled "Methods Of Treating Autoimmune Disease Via CTLA-4Ig," was duly and legally issued by the United States Patent and Trademark Office to Craig B. Thompson and Carl H. June on February 3, 2004.

9. The '941 patent is assigned to the University of Michigan and the United States of America as represented by the Secretary of the Navy.

10. Based on agreements with University of Michigan and United States Department of the Navy, Repligen is an exclusive licensee under the '941 patent and has the right to sue for infringement of the '941 patent.

COUNT I
DIRECT INFRINGEMENT OF THE '941 PATENT

11. Plaintiffs re-allege and incorporate herein by reference the allegations stated in paragraphs 1-10 of this Complaint.

12. Bristol-Myers filed or caused to be filed with the United States Food and Drug Administration ("FDA") a Biologic License Application ("BLA") #125118, seeking approval to market fusion protein abatacept for use in treating rheumatoid arthritis. Bristol-Myers has adopted the brand name ORENCIA® for abatacept.

13. On or about December 23, 2005, the FDA approved abatacept for the treatment of rheumatoid arthritis but not for any other use.

14. Using abatacept to treat rheumatoid arthritis infringes the '941 patent.

15. On information and belief, Bristol-Myers is manufacturing abatacept and contracting with others to manufacture abatacept to treat rheumatoid arthritis.

16. On information and belief, Bristol-Myers is importing, or contracting with others to import, abatacept to treat rheumatoid arthritis.

17. On information and belief, Bristol-Myers is selling and offering to sell abatacept to treat rheumatoid arthritis.

18. On information and belief, Bristol-Myers is instructing health care providers including doctors to administer abatacept to patients having rheumatoid arthritis.

19. On information and belief, Bristol-Myers is administering abatacept to patients having rheumatoid arthritis, or causing such administration.

20. Bristol-Myers now has made ORENCIA® commercially available for treating rheumatoid arthritis and, on information and belief, has for some time been making extensive preparation for offers for sale and sale of abatacept for the treatment of rheumatoid arthritis. For example, in the Form 10-Q Bristol-Myers filed with the Securities and Exchange Commission for the quarter ending September 30, 2005, BMS stated that abatacept already constituted a "significant proportion" of its $125 million inventory.

21. An actual and justiciable controversy exists, as Bristol-Myers's importation, use, offers to sell and selling abatacept is directly infringing the '941 patent.

COUNT II

CONTRIBUTORY AND INDUCEMENT OF INFRINGEMENT OF THE '941 PATENT

22. Plaintiffs re-allege and incorporate herein by reference the allegations stated in paragraphs 1-21 of this Complaint.

23. On information and belief, Bristol-Myers, by offering abatacept for sale for use in treating rheumatoid arthritis and/or by otherwise supplying abatacept for use in treating rheumatoid arthritis, is presently actively inducing infringement of and contributorily infringing the '941 patent, all to Plaintiffs' damage.

24. On information and belief, Bristol-Myers will continue to actively induce infringement of and contributorily infringe the '941 patent unless enjoined by this Court.

25. On information and belief, by administering abatacept to patients having rheumatoid arthritis, or causing such administration, Bristol-Myers infringes the '941 patent and will continue to infringe the '941 patent unless enjoined by this Court.

26. On information and belief, Bristol-Myers's infringement, active inducement of infringement, and contributory infringement have been willful and will continue to be willful, making this case exceptional and entitling Plaintiffs to increased damages and reasonable attorneys' fees pursuant to 35 U.S.C. §§ 284 and 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray that the Court enter judgment against Bristol-Myers:

(1) that Bristol-Myers's conduct in importing, using, offering to sell or selling abatacept for treatment of rheumatoid arthritis during the term of the '941 patent infringes, contributorily infringes, and actively induces the infringement of the '941 patent;

(2) that a permanent injunction is appropriate and proper, enjoining and restraining Bristol-Myers and its agents, servants, employees, affiliates, divisions, and subsidiaries, and those in association with them, from (a) unlicensed use of abatacept for treatment of rheumatoid arthritis; (b) unlicensed inducement of others to use abatacept for treatment of rheumatoid arthritis; and (c) unlicensed importation, offers to sell, or sales of abatacept for use in treating rheumatoid arthritis;

(5) an award of damages sufficient to compensate for such past infringement;

(6) an award of increased damages pursuant to 35 U.S.C. § 284;

(7) an award of all costs of this action, including attorneys' fees and interest; and

(8) such other and further relief, at law or in equity, to which Plaintiffs are justly entitled.

JURY DEMAND

Plaintiffs demand a jury trial on all issues triable by a jury.

Respectfully submitted,

Dated: December 21, 2006

By: /s/ Sam Baxter

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CERTIFICATE OF SERVICE

The undersigned certifies that a true and correct copy of the foregoing documents was served on counsel of record via the Court's ECF system on December 21, 2006.

/s/ Sam Baxter

IN THE UNITED STATES DISTRICT COURT FOR
THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

REPLIGEN CORPORATION and THE REGENTS OF THE UNIVERSITY OF MICHIGAN,	§	
Plaintiffs,	§	
v.	§	CIVIL ACTION NO.: 2:06-CV-004 JURY DEMANDED
BRISTOL-MYERS SQUIBB COMPANY,	§	
Defendant.	§	

DEFENDANT BRISTOL-MYERS SQUIBB COMPANY'S ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFFS' AMENDED COMPLAINT

Defendant Bristol-Myers Squibb Company ("Bristol-Myers") answers the allegations of the Amended Complaint filed by Plaintiffs Repligen Corporation and the Regents of the University of Michigan (collectively "Plaintiffs") as follows:

ANSWER

THE PARTIES

1. Bristol-Myers is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 1 of the Amended Complaint and accordingly these allegations are denied.

2. Bristol-Myers is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 2 of the Amended Complaint and accordingly these allegations are denied.

3. Bristol-Myers admits the allegations of Paragraph 3 of the Amended Complaint.

JURISDICTION AND VENUE

4. Bristol-Myers admits that the Amended Complaint alleges patent infringement arising under the Patent Laws of the United States but denies all remaining allegations of Paragraph 4 of the Amended Complaint.

5. Bristol-Myers admits that subject matter jurisdiction is proper in this Court under 28 U.S.C. §§ 1331 and 1338.

6. Bristol-Myers admits that the Court has personal jurisdiction over Bristol-Myers.

7. Bristol-Myers admits that venue is proper in this judicial district.

THE PATENT-IN-SUIT

8. Bristol-Myers admits that Craig B. Thompson and Carl H. June are the inventors named on the '941 patent. Bristol-Myers admits that the '941 patent issued on February 3, 2004. Bristol-Myers denies the remaining allegations of Paragraph 8 of the Amended Complaint.

9. Bristol-Myers admits that the assignees named on the face of the '941 patent are The Regents of the University of Michigan and The United States of America as represented by the Secretary of the Navy. Bristol-Myers is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 9 of the Amended Complaint and accordingly these allegations are denied.

10. Bristol-Myers is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 10 of the Amended Complaint and accordingly these allegations are denied.

COUNT I

DIRECT INFRINGEMENT OF '941 PATENT

11. Paragraph 11 of the Amended Complaint does not require a response.

12. Bristol-Myers admits the allegations of Paragraph 12 of the Amended Complaint.

13. Bristol-Myers admits that on or about December 23, 2005, the FDA approved abatacept solely for the treatment of rheumatoid arthritis.

14. Bristol-Myers denies the allegations of Paragraph 14 of the Amended Complaint.

15. Bristol-Myers admits that it is manufacturing abatacept and that it has contracted with others to manufacture abatacept. Bristol-Myers admits that it makes ORENCIA® commercially available for the treatment of rheumatoid arthritis. Bristol-Myers otherwise denies all remaining allegations of Paragraph 15 of the Amended Complaint.

16. Bristol-Myers denies the allegations of Paragraph 16 of the Amended Complaint.

17. Bristol-Myers admits that it is selling and offering to sell abatacept to treat rheumatoid arthritis in the manner approved by the FDA. Bristol-Myers otherwise denies all remaining allegations of Paragraph 17 of the Amended Complaint.

18. Bristol-Myers admits that it makes ORENCIA® commercially available for the treatment of rheumatoid arthritis and provides medical practitioners with information on the use of ORENCIA® in the manner approved by the FDA. Bristol-Myers otherwise denies all remaining allegations of Paragraph 18 of the Amended Complaint.

19. Bristol-Myers admits that it makes ORENCIA® commercially available for the treatment of rheumatoid arthritis but otherwise denies all remaining allegations of Paragraph 19 of the Amended Complaint.

20. Bristol-Myers admits that it makes ORENCIA® commercially available for the treatment of rheumatoid arthritis. Bristol-Myers admits that it has for some time been making preparation for offers for sale and sale of abatacept for the treatment of rheumatoid arthritis. Bristol-Myers admits that its Form 10-Q for the quarter ending September 30, 2005, states that abatacept constituted a "significant portion" of Bristol-Myers' $125 million inventory. Bristol-Myers otherwise denies the remaining allegations of Paragraph 20 of the Amended Complaint**.**

21. Bristol-Myers denies the allegations of Paragraph 21 of the Amended Complaint.

COUNT II

CONTRIBUTORY AND INDUCEMENT OF INFRINGEMENT OF '941 PATENT

22. Paragraph 22 of the Amended Complaint does not require a response.

23. Bristol-Myers denies the allegations of Paragraph 23 of the Amended Complaint.

24. Bristol-Myers denies the allegations of Paragraph 24 of the Amended Complaint.

25. Bristol-Myers denies the allegations of Paragraph 25 of the Amended Complaint.

26. Bristol-Myers denies the allegations of Paragraph 26 of the Amended Complaint.

PRAYER FOR RELIEF

27. Bristol-Myers denies that Plaintiffs are entitled to any of the relief requested in Paragraphs 1, 2, and 5-8 under the heading "Prayer for Relief" in the Amended Complaint.

28. Bristol-Myers denies all allegations not expressly admitted or expressly responded to herein.

FIRST AFFIRMATIVE DEFENSE - COLLATERAL ESTOPPEL

29. On August 17, 2000, Plaintiffs Repligen and the Regents of the University Of Michigan, sued Bristol-Myers in the Eastern District of Michigan, in an action styled The

University of Michigan and Repligen Corporation v. Bristol-Myers Squibb Co. and identified as Civil Action No. 00-CV-73690 (The "Michigan Litigation").

30. In the Michigan Litigation, Repligen and the University of Michigan asserted that Craig Thompson was either a sole and/or a co-inventor of United States Patent Nos. 5,434,131 ("the '131 patent"), 5,844,095 ("the '095 patent"), 5,851,795 ("the '795 patent"), 5,885,579 ("the '579 patent"), 5,968,510 ("the '510 patent"), 5,977,318 ("the '318 patent"), and 5,885,796 ("the '796 patent"), which claimed, *inter alia*, the compound CTLA4-Ig and its use as an immunosuppressant.

31. Trial in the Michigan Litigation was held in April and May 2003 before the Honorable George Caram Steeh. Craig Thompson testified in that trial as a witness for Repligen and the University of Michigan.

32. Judge Steeh heard both fact and expert evidence on what CTLA4-Ig is, how it functions to regulate and suppress the immune system and its use to block T-cell and B-cell interactions.

33. On September 10, 2003, Judge Steeh issued his twenty-seven page detailed decision, reported at 301 F.Supp.2d 633, in which he made the following findings, among others:

i. It was Bristol-Myers scientists, not Craig Thompson, who discovered that B7 was a natural ligand for CD28 and CTLA4.

ii. It was Bristol-Myers scientists, not Craig Thompson, who were the first to make a functional CTLA-4Ig fusion protein.

iii. It was Bristol-Myers scientists, not Craig Thompson, who were the first to determine that a functional CTLA-4Ig fusion protein bound a naturally-occurring ligand known

as B7 with much higher affinity (binding strength) than did CD28, which is a surface protein present on T-cells.

iv. It was Bristol-Myers scientists, not Craig Thompson, who were the first to determine that a functional CTLA-4Ig fusion protein could be used to regulate T-cell interactions.

34. Judge Steeh found that the Bristol-Myers scientists were the only inventors of, *inter alia*, the following patent claims, and that Craig Thompson had not made any inventive contribution to any of those inventions:

i. Claim 1 of the '131 patent: A method for regulating functional CTLA4 positive T cell interactions with B7 positive cells comprising contacting said B7 positive cells with a B7 ligand to interfere with reaction of B7 antigen with CTLA4, wherein said B7 ligand is a fusion protein that contains a portion of the extracellular domain of CTLA4, which portion binds B7.

ii. Claim 5 of the '131 patent: A method for treating immune system diseases mediated by T cell interactions with B7 positive cells comprising administering to a subject a B7 ligand to regulate T cell interactions with said B7 positive cells wherein said B7 ligand is a fusion protein that contains a portion of the extracellular domain of CTLA4, which portion binds B7. Claim 6 of the '131 patent: The method of claim 5, wherein said ligand is CTLA4Ig fusion protein.

iii. Claim 1 of the '579 patent: A method for regulating functional CTLA4 positive T cell interactions with B7 positive cells comprising contacting the B7 positive cells with a ligand for the B7 antigen, in a amount effective to interfere with reaction of endogenous B7 antigen with CTLA4, wherein the ligand is a soluble CTLA4 molecule.

iv. Claim 4 of the '579 patent: A method for treating immune system diseases mediated by T cell interactions with B7 positive cells comprising administering to a subject a ligand for B7 antigen, in an amount effective to regulate T cell interactions with said B7 positive cells.

35. Repligen and the University of Michigan appealed Judge Steeh's decision to the Court of Appeals for the Federal Circuit. That court heard argument on July 9, 2004, and summarily affirmed Judge Steeh on July 12, 2004. That decision is now final.

36. As a result of the Michigan Litigation, it has been conclusively determined that Bristol-Myers scientists, and not any person from whom Repligen or the University of Michigan can claim rights, are the true and prior inventors of CTLA4-Ig and its use to regulate B-cell and T-cell mediated immune responses.

37. Repligen, the University of Michigan, and Bristol-Myers are the same entities that were parties in the Michigan Litigation.

38. Repligen and the University of Michigan had a full and fair opportunity to litigate the issues in the Michigan Litigation.

39. Repligen and the University of Michigan are collaterally estopped from relitigating the fact findings made by Judge Steeh in his decision in the Michigan Litigation, attached hereto as Exhibit A.

SECOND AFFIRMATIVE DEFENSE - INVALIDITY

40. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 102.

41. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 103.

42. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 112.

43. The '941 patent fails to meet, and each claim of the '941 patent fails to meet, one or more conditions of patentability specified in Part II of Title 35 of the United States Code.

THIRD AFFIRMATIVE DEFENSE - UNENFORCEABILITY

44. Each and every claim of the '941 patent is unenforceable as a result of inequitable conduct during the prosecution of the '941 patent.

45. Each individual associated with the filing or prosecution of a patent application, including attorneys, has a duty of candor and good faith in dealing with the Patent Office. An individual breaches that duty when, with an intent to deceive the patent examiner, the individual fails to disclose to the Patent Office all information known to be material to the patentability of the claimed invention or misstates material information. A breach of a patent applicant's duty of candor renders unenforceable all claims which eventually issue from the application in connection with which such breach occurred and all claims that issue from any related applications.

46. All claims of the '941 patent are unenforceable because one or more individuals associated with the filing and/or prosecution of the '941 patent ("Applicants") committed inequitable conduct during the prosecution of the '941 patent.

47. Bristol-Myers realleges the allegations of Paragraphs 29-39 above.

48. Applicants knew of, but withheld from the Patent Examiner that Judge Steeh had decided the Michigan Litigation adversely to them and had rejected their claim that Craig Thompson was an inventor of CTLA4-Ig and its use to regulate immune responses.

49. The fact that Bristol-Myers, and not any person from whom Repligen or the University of Michigan claims rights, made those inventions, was material to the prosecution of

the '941 patent, and Applicants withheld that information from the Patent Examiner with the intent to deceive.

50. Applicants also knew, and withheld from the Patent Office, the facts that the inventors named in the '941 patent had obtained and used information obtained from Bristol-Myers on CTLA4-Ig, its properties, and its use in regulating immune responses. On information and belief, information that Applicants obtained from Bristol-Myers and about Bristol-Myers' activities relating to CTLA4-Ig was at least part of their motivation to insert claims to the treatment of autoimmune diseases in the applications that led to the '941 patent.

51. Applicants also committed inequitable conduct by failing to disclose material prior art references to the Patent Office during the prosecution of the '941 patent, including Peter S. Linsley, et al., *Immunosuppression In Vivo by a Soluble Form of the CTLA-4 T Cell Activation Molecule*, 257 SCIENCE 792 (Aug. 7, 1992) ("Linsley article") and Deborah J. Lenschow, et al., *Long-Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4-Ig*, 257 SCIENCE 789 (Aug. 7, 1992) ("Lenschow article"). At least one of the individuals associated with the filing or prosecution of the '941 patent knew of these prior art references and of their materiality during the prosecution of the '941 patent but did not disclose them to the Patent Office, as set forth below.

52. In August 1992, the Linsley and Lenschow articles were both published in Science.

53. The Linsley article discloses *in vivo* testing in which CTLA4-Ig was effective as an immunosuppressant.

54. The Lenschow article also discloses *in vivo* testing in which CTLA4-Ig was effective as an immunosuppressant.

55. In November 1992, an article entitled "T-cell activation by the CD28 ligand B7 is required for cardiac allograft rejection *in vivo*" was published in the Proceedings of the National Academy of Sciences. Laurence A. Turka, et al., 89 PROC. NAT'L ACAD. SCI. 11102 (Nov. 1992). This article was co-authored by Craig Thompson – one of the inventors named in the '941 patent – and cites both the Linsley and Lenschow articles.

56. On information and belief, Craig Thompson had access to, and knew of the existence and content of the Linsley and Lenschow articles before those articles were submitted to Science for publication. Because those articles were cited in the Turka et al. article, Craig Thompson knew of them by at least November 1992.

57. On November 10, 1994, Repligen filed United States Patent Application No. 08/337,960 ("the '960 application"). The PCT Application corresponding to the '960 application (International Publication No. WO96/14865), was published and its specification cites the Lenschow article.

58. On February 2, 1996, Repligen filed another patent application that led to U.S. Patent No. 6,444,792 (the "Repligen '792 patent"). The specification of the Repligen '792 patent refers to the Linsley article.

59. The Lenschow article was cited on the face of the Repligen '792 patent during the pendency of the '941 patent before the Patent Office.

60. Individuals employed by Repligen who were associated with the filing and/or prosecution of the '941 patent knew of the Linsley and Lenschow articles by at least February 2, 1996.

61. On September 25, 1996, the Patent Examiner of the '941 patent rejected pending claims of the application as being anticipated by the '131 patent, assigned to Bristol-Myers. The

rejected claims were directed to a method of treating a patient having an autoimmune disease by administering "a ligand which binds a naturally occurring CD28 stimulatory ligand." A rejected dependent claim specified that the ligand was CTLA4-Ig.

62. In response to the rejection, on March 25, 1997, Applicants canceled all of the claims that referred to CTLA4-Ig and amended the remaining claims to limit them to the use of "a fragment of an anti-CD28 antibody" instead of the use of "a ligand which binds a naturally occurring CD28 stimulatory ligand." As a result of that amendment, the application no longer contained claims to the use of CTLA4-Ig for the treatment of any autoimmune disease.

63. After about four more years of prosecution, on June 4, 2001, Applicants added back claims that eventually issued as the claims of the '941 patent directed to methods of treatment using CTLA4-Ig. In the amendment, Applicants told the Patent Examiner that the '131 patent:

> merely demonstrates that CTLA-4Ig is an inhibitor of *in vitro* immune responses dependent upon cellular interactions and suggests *in vivo* applications for immune system diseases. [The '131 patent] clearly does not teach or enable methods for treating MS, SLE, RA and scleroderma by administering CTLA-4Ig. In fact, [the '131patent] doesn't even mention these diseases. Moreover, at column 25, lines 6-11, [the '131 patent] states:
>
> > "The immunosuppressive effects of CTLA4-Ig *in vitro* suggest that ***future investigations are warranted*** into possible therapeutic effects of this molecule for treatment of autoimmune disorders involving aberrant T cell activation or Ig production." (emphasis added)
>
> [The '131 patent] therefore actually admits that it does not enable the presently claimed methods.

64. Applicants withheld the Linsley and Lenschow articles from the Patent Office. The Linsley and Lenschow articles are each material and not cumulative because each discloses

in vivo data to show the immunosuppressive effects of CTLA4-Ig. The Linsley article states at page 794:

> We demonstrated that CTLA4Ig is a potent immunosuppressive agent in vivo, in agreement with previous in vitro results...Our data suggest that CTLA4Ig has attractive features for an immunosuppressive drug (that is, in vivo stability, low toxicity, and high specificity)...Our results showing that CTLA4Ig also suppressed humoral response suggest potential uses of CTLA4Ig in the treatment of Ab-mediated autoimmune diseases.

In addition, the Lenschow article states at page 792:

> The capacity of CTLA4Ig to significantly prolong human islet graft survival in mice in a donor-specific manner suggests that blocking the interaction of costimulatory molecules such as CD28-B7 may provide an approach to immunosuppression.

65. Applicants argued to the Patent Office that there was a lack of *in vivo* prior art data demonstrating the immunosuppressive effects of CTLA4-Ig when they were fully aware of the existence of the Linsley and Lenschow articles, which supplied that information, as well as the relationship between the *in vivo* data and the use of CTLA4-Ig for the treatment of autoimmune diseases.

66. Applicants withheld the Linsley and Lenschow articles with an intent to mislead the Patent Office. By failing to disclose the Linsley and Lenschow articles, Applicants misled the Patent Examiner regarding the disclosure of *in vivo* testing which demonstrated the immunosuppressive effects of CTLA4-Ig and its use to treat autoimmune diseases in the prior art.

67. Applicants committed inequitable conduct by failing to disclose to the Patent Examiner testimony by Craig Thompson, as well as Damle et al., *Direct helper T-cell-induced B cell differentiation involves interaction between T cell antigen CD28 and B cell activation antigen B7,* 21 EURO. J. IMMUNOL. 1277 (1991) ("Damle").

68. Applicants' statement in their June 4, 2001, amendment (quoted above) that the '131 patent "does not even mention these diseases" was misleading, because Applicants knew that persons of ordinary skill in the art were aware that multiple sclerosis and rheumatoid arthritis were commonly known to be autoimmune diseases.

69. Craig Thompson testified under oath in the Michigan Litigation that:

> Q. And one of the examples of autoimmune diseases that you gave ways [sic] rheumatoid arthritis?
>
> A. Yes.
>
> Q. And would other examples of autoimmune diseases would be things like multiple sclerosis or organ transplant complications?
>
> A. Yes.
>
> Q. And for [sic] all those things known to be autoimmune diseases in the 1990 time frame?
>
> A. I believe most people believe there [sic] were autoimmune diseases during that time, yes.

Thompson Tr., May 1, 2003, page 1, line 17 - page 2, line 2.

70. On information and belief, Applicants were aware that Damle specifically identified rheumatoid arthritis and systemic lupus erythematosus ("SLE") as autoimmune diseases that could be treated by regulating CD28/B7 interactions using molecules that target CD28 and B7.

71. The '131 patent and the Linsley article disclosed that CTLA4-Ig targeted B7.

72. The Thompson testimony and Damle article were material because each evidences that a person of ordinary skill in the art would have understood that rheumatoid arthritis and SLE were examples of the autoimmune diseases referred to in the '131 patent,

which the Patent Examiner had relied on to reject the claims, and which Applicants distinguished by arguing that it did not identify any autoimmune disease.

73. On information and belief, Applicants' failure to disclose the Thompson testimony and the Damle reference were made with the intent to mislead the Patent Office regarding the scope of the teaching in the '131 patent.

74. On information and belief, Applicants were aware that statements in their specification and statements made to the Patent Office about Example XVI of the '941 patent were unfounded, false and misleading.

75. Applicants made the following representations to the Patent Office regarding the predictive ability of the EAE model of Example XVI in treating autoimmune disease in humans:

(i) Applicants represented in their '941 patent specification that:

> "Experimental Autoimmune Encephalomyelitis (EAE) is a rodent and primate model for multiple sclerosis." (column 47, lines 66-67). "As shown in FIG. 22, mice receiving huCTLA-4Ig-treated cells (designated PPIB CTLA-4) showed a significantly reduced severity of their first episode of disease as compared to mice receiving untreated cells (designated PPIA control). In addition, ensuing relapses in the mice receiving huCTLA-4Ig-treated cells were less severe than in mice receiving cells not exposed to huCTLA-4Ig. In fact, all five mice receiving huCTLA-4Ig-treated cells stopped relapsing, and no longer showed signs of disease at 80-100 days post transfer." (column 48, lines 31-41).
>
> "Clinical disease severity was reduced even further by treating both the donor mice and the cultured cells with huCTLA-4Ig (FIG. 23)." (column 48, lines 42-44).
>
> "Treatment of either the donor mice or the in vitro cultures resulted in significantly reduced clinical disease severity. Treatment of both the donor mice and the cultured cells with huCTLA-4Ig was the most effective protocol for reducing clinical disease severity." (column 48, lines 51-55).
>
> "Direct administration of huCTLA-4Ig to mice receiving adoptively transferred cells was also examined. As shown in FIG. 24, when PLSJLFI/J recipient mice were given 100 μg of either huCTLA-4Ig or human lgG in PBS intraperitoneally on days 1 to 9 post transfer, no

difference in disease severity was observed between the two groups of mice. However, in experiments utilizing SJL/J mice, reduced disease severity during relapse was noted in mice treated with 100 μg huCTLA-4Ig intraperitoneally on days 1 to 5 post transfer (FIG. 25)." (column 48, lines 56-65).

"Administration of huCTLA-4Ig markedly reduced the mean clinical severity of disease in these animals, as compared to the mice treated with lgG1. These findings indicate that direct administration of soluble human huCTLA-4Ig can provide an effective therapeutic strategy in the treatment of autoimmune disease." (column 49, lines 34-39).

(ii) Applicants represented to the Patent Office:

On May 19, 1994, that: "Further, Applicants' specification shows that autoimmune disease can be treated in a subject by administering to the subject a selected inhibitory ligand that binds a natural stimulatory ligand to CD28. *See*, Specific Example XVI and Figs. 22-27, showing for example in an accepted *in vivo* murine model for the autoimmune disease multiple sclerosis that the clinical severity of the disease state can be reduced by administration of a soluble CTLA-4 (huCTLA-4Ig).

The examples in Applicants' specification employ model systems that are acceptable, in view of Applicants' disclosure taken as a whole, as being reasonably predictive of having the state utility."

On November 21, 1995 that: Example XVI provides one basis of support for the addition of the new claims. Claim 25 is a representative claim as follows: A method of treating a patient having an autoimmune disease comprising administering to the patient a ligand which binds a naturally occurring CD28 stimulatory ligand in an amount effective to suppress the patient's immune response.

On August 7, 1998 and May 6, 1999, that: "Applicants also refer the Examiner to Specific Example XVI of the present specification, describing the efficacy of CTLA4-Ig in an adoptively transferred EAE and direct EAE murine model. Although these studies employ CTLA4-Ig, due to the essential nature of CD28 in the stimulatory pathway, one skilled in the art after learning of the primate study and the murine EAE model studies, and in light of the superantigen murine model studies, could heuristically conclude that the claimed methods utilizing anti-CD28 antibody fragments would be effective in treating autoimmune disease in humans."

On June 4, 2001, that: "Applicants submit that one skilled in the art, after reading the specification, would be able to make and use the now claimed invention. In particular, Applicants refer the Examiner to Specific

> Example XVI which describes the effective use of CTLA-4Ig in an adoptively transferred EAE and direct EAE murine model. As discussed at the interview, Applicants specifically draw the Examiner's attention to Figure 27 which shows that in a direct (active) model of EAE, CTLA-4Ig is not only effective at reducing the mean clinical severity at the onset of disease (e.g. days 10-25), but is extremely effective in reducing the mean clinical severity of disease when disease is ***ongoing*** (e.g. days 25-45)."

76. Applicants knew those statements were false and that the EAE model did not accurately reflect a human therapeutic situation.

77. The claims of the '941 patent are directed to treating autoimmune diseases, specifically rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and scleroderma in patients.

78. Contrary to the affirmative representations that Applicants made in the specification and in their arguments to the Patent Examiner, Applicants knew that their EAE data did not show any significant efficacy in reducing either the progression or the severity of the experimental disease.

79. On information and belief, Applicants knew, but did not tell the Patent Examiner, that the EAE test of Example XVI was (a) not a predictor of efficacy in treating multiple sclerosis in humans and (b) not a predictor of efficacy in treating any of the other autoimmune diseases recited in the claims of the '941 patent, and specifically not a predictor of efficacy in treating rheumatoid arthritis.

80. The '941 patent contains no *in vivo* data and no *in vivo* animal models that are indicators of efficacy in treating rheumatoid arthritis.

81. Applicants knew those material misstatements were relevant to the review of their patent application by the Patent Office because their claims had been rejected as not enabled in Official Actions dated August 7, 1997, November 6, 1998, December 2, 2000, and January 15,

2002. On information and belief, Applicants' misstatements were made with intent to mislead the Patent Office concerning the ability of the EAE model to predict treatment for human diseases when in fact the EAE model does not predict treatment for any human disease.

82. Each and every claim of the '941 patent is unenforceable as a result of Applicants deceptively failing to name the proper inventors.

83. On February 17, 1992, Dr. Laurence Turka and Dr. Craig Thompson of Plaintiff University of Michigan submitted a research proposal to Bristol-Myers to perform *in vivo* cardiac allograft experiments using CTLA4-Ig supplied by Bristol-Myers ("Research Proposal", Exhibit B).

84. The Research Proposal included the following work to be performed by the University of Michigan:

i. Determining the optimal means of administering CTLA4-Ig, in part, by administering CTLA4-Ig at less than 500 μg/day for seven days.

ii. Defining the immunologic mechanism by which CTLA4-Ig prevents allograft rejection, in part, by performing thymectomies on animals prior to transplantation.

85. Under the Research Proposal, it was understood that Bristol-Myers would supply the CTLA4-Ig used in the work.

86. Upon information and belief, the work identified above in Paragraph 84 went forward in good faith before a formal agreement was executed.

87. The Research Proposal was formalized into an agreement dated April 16, 1992 ("Research Agreement", Exhibit C).

88. Under the Research Agreement, Bristol-Myers and the University of Michigan agreed to collaborate in research related to CTLA4-Ig. (Exhibit C at 1).

89. Under the Research Agreement, Bristol-Myers agreed to fund the University of Michigan to perform *in vivo* cardiac allograft experiments. (Exhibit C at ¶ 5).

90. Upon information and belief, Dr. Turka performed the *in vivo* cardiac allograft experiments that were the subject of the Research Proposal and Research Agreement.

91. While Dr. Thompson was originally named in the Research Agreement as a project director in the paragraph entitled "Key Personnel", his name was crossed off. (Exhibit C at ¶ 3).

92. The work performed pursuant to the Research Proposal is disclosed and relied on in the '941 patent, in Example X.

93. The Applicants relied on Example X during prosecution of the '941 patent. For example:

> Applicant submits that the pending claims are fully enabled and one skilled in the art would be able to make and use the claimed invention without undue experimentation. At the outset, Applicant incorporates herein the arguments set forth in the prior responses.

(July 19, 2002 After Final Response Under 37 C.F.R. §1.116 at 2).

> Applicants have added new Claims 39-48. Support for the new claims may be found throughout the application and in particular, without limitation, . . . Specific Examples X and XVI.

(May 10, 1999 Amendment and Response at 3).

> Applicants have cancelled Claims 1-24 and have added new Claims 25-34. Bases for the new claims may be found throughout the application as filed and in particular, without limitation, . . . Specific Examples X and XVI.

(November 21, 1995 Preliminary Amendment at Remarks).

94. Upon information and belief, Dr. Turka performed the *in vivo* cardiac experiments identified above in Paragraph 84 that are disclosed in and relied on in the '941 patent.

95. Upon information and belief, Applicants did not name Dr. Turka as an inventor on the '941 patent with deceptive intent.

FOURTH AFFIRMATIVE DEFENSE - NONINFRINGEMENT

96. Bristol-Myers does not and will not infringe, contributorily infringe, or induce the infringement of any valid claim of the '941 patent either by literal infringement or by infringement under the doctrine of equivalents.

97. To the extent applicable, Bristol-Myers' activities are immunized from a claim of infringement by 35 U.S.C. § 271(e)(1).

FIFTH AFFIRMATIVE DEFENSE – LICENSE

98. The allegations set forth in Paragraphs 83-94 are incorporated herein by reference.

99. The Research Agreement was signed on behalf of the University of Michigan by Paul J. Stemple (Manager, Office of Contract Administration) and was acknowledged by University of Michigan personnel Dr. Turka, Dr. Hua Lin, and Dr. Steven Bolling. (Exhibit C at 4). The Research Agreement was signed on behalf of Bristol-Myers by Ingegerd Hellstrom, Vice President Exploratory Biomedical Research. (*Id.*).

100. The Research Agreement granted Bristol-Myers a royalty-free license to each useful discovery resulting from the research program between Bristol-Myers and the University of Michigan:

> Invention Rights:
>
> A. Any and all data, samples, discoveries, inventions, improvements, trade secrets and the like, whether patentable or unpatentable, conceived or made by [University of Michigan] emanating from or relating to [University of Michigan's] services and [Bristol-Myers'] materials under this Agreement, shall be the joint property of the parties. In consideration of [Bristol-Myers'] contributions to the research program, [University of Michigan] hereby grants to [Bristol-Myers] a non-exclusive worldwide royalty-free license to each useful discovery, whether patentable or unpatentable.

(Exhibit C at ¶ 7).

101. If and to the extent the subject matter that is claimed in the '941 patent is a useful discovery, it falls within that grant.

102. Accordingly, Bristol-Myers holds a royalty-free license from Plaintiff University of Michigan under the '941 patent.

SIXTH AFFIRMATIVE DEFENSE – OWNERSHIP

103. The allegations set forth in Paragraphs 83-94 and 99-101 are incorporated herein by reference.

104. The Research Agreement provides that any and all discoveries and inventions conceived or made by the University of Michigan emanating from or relating to the University of Michigan's services and Bristol-Myers' materials under the Research Agreement shall be the joint property of the parties.

105. The claimed invention in the '941 patent emanated from and/or related to Bristol-Myers' materials under the Research Agreement.

106. Pursuant to the Research Agreement, the University of Michigan and Bristol-Myers jointly own the '941 patent.

BRISTOL-MYERS' COUNTERCLAIMS

107. Bristol-Myers is a corporation recognized and existing under the laws of the state of Delaware, with its principal place of business at 345 Park Avenue, New York, NY 10154-0037.

108. Plaintiff Repligen Corporation alleges that it is a corporation organized under the laws of the state of Delaware, with its principal place of business at 41 Seyon Street, Building #1, Suite 100, Waltham, MA 02453.

109. Plaintiff University of Michigan alleges that it is a constitutional corporation of the state of Michigan located in Ann Arbor, Michigan.

110. These counterclaims are for declaratory judgment relief arising under 28 U.S.C. §§ 2201 and 2202, and for noninfringement, invalidity, and unenforceability under the patent laws of the United States, 35 U.S.C. § 101, *et seq*.

111. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331, 1338(a), 1367 and 2201.

112. Venue is proper in this district because Plaintiffs filed suit against Bristol-Myers in this district.

COUNT I

DECLARATORY JUDGMENT OF INVALIDITY OF THE '941 PATENT

113. Bristol-Myers incorporates by reference the allegations made in Paragraphs 107-112 above, of Bristol-Myers' Counterclaims.

114. An actual controversy exists between Bristol-Myers and Plaintiffs over the alleged validity of United States Patent No. 6,685,941 ("the '941 patent").

115. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 102.

116. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 103.

117. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 112.

118. All claims of the '941 patent are invalid in light of their failure to meet one or more conditions of patentability specified in Part II of Title 35 of the United States Code.

COUNT II

DECLARATORY JUDGMENT OF NONINFRINGEMENT OF THE '941 PATENT

119. Bristol-Myers incorporates by reference the allegations made in Paragraphs 107-112 above, of Bristol-Myers' Counterclaims.

120. An actual controversy exists between Bristol-Myers and Plaintiffs over the alleged infringement of the '941 patent.

121. Bristol-Myers does not infringe, contributorily infringe, or induce the infringement of any valid claim of the '941 patent either by literal infringement or by infringement under the doctrine of equivalents.

COUNT III

DECLARATORY JUDGMENT OF UNENFORCEABILITY OF THE '941 PATENT

122. Bristol-Myers incorporates by reference the allegations made in Paragraphs 107-112 above, of Bristol-Myers' Counterclaims.

123. Bristol-Myers repeats and realleges each of the allegations of Paragraphs 29-95 above.

124. An actual controversy exists between Bristol-Myers and Plaintiffs over the alleged enforceability of the '941 patent.

125. Each and every claim of the '941 patent is unenforceable as a result of inequitable conduct during the prosecution of the '941 patent. The inequitable conduct is detailed in Paragraphs 44-95 above.

COUNT IV

DECLARATORY JUDGMENT THAT BRISTOL-MYERS HAS A ROYALTY-FREE LICENSE TO PRACTICE THE '941 PATENT AND A RIGHT OF OWNERSHIP TO THE '941 PATENT

126. Bristol-Myers incorporates by reference the allegations made in Paragraphs 107-112 above, of Bristol-Myers' Counterclaims.

127. Bristol-Myers repeats and realleges each of the allegations of Paragraphs 83-94, 99-101 and 104-105 above.

128. Subject matter jurisdiction for this claim exists under 28 U.S.C. § 2201 and principles of pendent jurisdiction. There exists an actual controversy between Bristol-Myers and Plaintiffs with respect to Bristol-Myers' rights under the "Invention Rights" provision of the Research Agreement.

129. Bristol-Myers holds a royalty-free license under the '941 patent and is entitled to a declaration to that effect.

130. Bristol-Myers holds a right of ownership to the '941 patent and is entitled to a declaration to that effect.

COUNT V

BREACH OF CONTRACT

131. Bristol-Myers incorporates by reference the allegations made in Paragraphs 107-112 and 128 above, of Bristol-Myers' Counterclaims.

132. Bristol-Myers repeats and realleges each of the allegations of Paragraphs 83-94, 99-101, and 104-105 above.

133. The Research Agreement (see Exhibit C) is a binding and legally enforceable contract supported by adequate consideration.

134. Bristol-Myers has fully performed all of its obligations under the Research Agreement.

135. Plaintiff University of Michigan has inexcusably and materially breached the Research Agreement by asserting the '941 patent against Bristol-Myers and participating in this litigation.

136. As a direct and proximate result of Plaintiff University of Michigan's breach of the Research Agreement, Bristol-Myers has suffered, and will suffer, damages.

EXCEPTIONAL CASE AND ATTORNEYS' FEES

137. As a result of Applicants' inequitable conduct and because Plaintiffs brought this suit knowing the '941 patent is invalid and unenforceable, this is an exceptional case such that Bristol-Myers is entitled to an award of its reasonable attorneys' fees, as provided by 35 U.S.C. §285.

DEMAND FOR JURY TRIAL

138. Bristol-Myers demands trial by jury on all affirmative defenses, counterclaims, and issues triable by jury.

PRAYER FOR RELIEF

139. For the reasons set forth above, Bristol-Myers prays for the Court's judgment that:

(a) the '941 patent is invalid and each claim of the '941 patent is invalid;

(b) Bristol-Myers has not infringed any valid claim of the '941 patent;

(c) the '941 patent is not enforceable;

(d) Bristol-Myers has a royalty-free license under the '941 patent;

(e) Bristol-Myers is an owner of the '941 patent;

(f) Plaintiffs' Amended Complaint be dismissed with prejudice;

(g) Plaintiffs take nothing by reason of their claims against Bristol-Myers;

(h) costs of this action be assessed against Plaintiffs;

(i) awards Bristol-Myers damages in an amount to be proved at trial;

(j) awards Bristol-Myers any and all pre-judgment and post-judgment interest to which it is entitled;

(k) awards Bristol-Myers its reasonable attorneys' fees; and

(l) awards Bristol-Myers such other and further relief at law or equity as the Court may deem just and proper.

Respectfully submitted,

/s/ Robert L. Baechtold (by Wesley Hill w/ permission)

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFFS' AMENDED COMPLAINT was served by facsimile and/or by the Court's electronic service to all known attorneys of record on this the 11th day of January, 2007 as follows:

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/s/ Wesley Hill

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

REPLIGEN CORPORATION and THE REGENTS OF THE UNIVERSITY OF MICHIGAN,

Plaintiffs,

v.

BRISTOL-MYERS SQUIBB COMPANY,

Defendant.

Case No. 2:06-cv-4-TJW

ANSWER OF PLAINTIFFS REPLIGEN CORPORATION AND THE REGENTS OF THE UNIVERSITY OF MICHIGAN TO DEFENDANT BRISTOL-MYERS SQUIBB COMPANY'S AMENDED COUNTERCLAIMS

Plaintiffs Repligen Corporation ("Repligen") and The Regents of the University of Michigan ("University of Michigan") (collectively "Plaintiffs"), by and through the undersigned attorneys, submit the following Answer to the counterclaims in Defendant Bristol-Myers Squibb Company's Amended Answer, Affirmative Defenses, and Counterclaims ("Defendant's Amended Answer").

ANSWER TO AMENDED COUNTERCLAIMS

Defendant's counterclaims begin with paragraph 101 and refer back to other paragraphs in Defendant's Amended Answer. Plaintiffs respond below in the order of Defendant's recitals:

101. Bristol-Myers is a corporation recognized and existing under the laws of the state of Delaware, with its principal place of business at 345 Park Avenue, New York, NY 10154-0037.

ANSWER: Paragraph 101 of Defendant's Amended Answer does not require an answer.

102. Plaintiff Repligen Corporation alleges that it is a corporation organized under the laws of the state of Delaware, with its principal place of business at 41 Seyon Street, Building #1, Suite 100, Waltham, MA 02453.

ANSWER: Plaintiffs admit the allegations of paragraph 102.

103. Plaintiff University of Michigan alleges that it is a constitutional corporation of the state of Michigan located in Ann Arbor, Michigan.

ANSWER: Plaintiffs admit the allegations of paragraph 103.

104. These counterclaims are for declaratory judgment relief arising under 28 U.S.C. §§ 2201 and 2202, and for noninfringement, invalidity, and unenforceability under the patent laws of the United States, 35 U.S.C. § 101, et seq.

ANSWER: Plaintiffs admit only that Defendant's Amended Answer includes a request for declaratory judgment relief arising under 28 U.S.C. §§ 2201 and 2202, and for noninfringement, invalidity, and unenforceability under the patent laws of the United States, 35 U.S.C. § 101, et seq., and deny all remaining allegations.

105. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331, 1338(a), 1367 and 2201.

ANSWER: Plaintiffs admit the allegations of paragraph 105.

106. Venue is proper in this district because Plaintiffs filed suit against Bristol-Myers in this district.

ANSWER: Plaintiffs admit the allegations of paragraph 106.

COUNT I

DECLARATORY JUDGMENT OF INVALIDITY OF THE '941 PATENT

107. Bristol-Myers incorporates by reference the allegations made in paragraphs 101-106, above, of Bristol-Myers' Counterclaims.

ANSWER: Plaintiffs incorporate by reference their answer to paragraphs 101-106 from above.

108. An actual controversy exists between Bristol-Myers and Plaintiffs over the alleged validity of United States Patent No. 6,685,941 ("the '941 patent").

ANSWER: Plaintiffs admit the allegations of paragraph 108.

109. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 102.

ANSWER: Plaintiffs deny the allegations of paragraph 109.

110. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 103.

ANSWER: Plaintiffs deny the allegations of paragraph 110.

111. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 112.

ANSWER: Plaintiffs deny the allegations of paragraph 111.

112. All claims of the '941 patent are invalid in light of their failure to meet one or more conditions of patentability specified in Part II of Title 35 of the United States Code.

ANSWER: Plaintiffs deny the allegations of paragraph 112.

COUNT II

DECLARATORY JUDGMENT OF NON-INFRINGEMENT OF THE '941 PATENT

113. Bristol-Myers incorporates by reference the allegations made in paragraphs 101-106, above, of Bristol-Myers' Counterclaims.

ANSWER: Plaintiffs incorporate by reference their answer to paragraphs 101-106 from above.

114. An actual controversy exists between Bristol-Myers and Plaintiffs over the alleged infringement of the '941 patent.

ANSWER: Plaintiffs admit the allegations of paragraph 114.

115. Bristol-Myers does not infringe, contributorily infringe, or induce the infringement of any valid claim of the '941 patent either by literal infringement or by infringement under the doctrine of equivalents.

ANSWER: Plaintiffs deny the allegations of paragraph 115, and expressly incorporate by reference and re-allege herein paragraphs 12-20 and 22-26 of Plaintiffs' Amended Complaint.

COUNT III

DECLARATORY JUDGMENT OF UNENFORCEABILITY OF THE '941 PATENT

116. Bristol-Myers incorporates by reference the allegations made in paragraphs 101¬106, above, of Bristol-Myers' Counterclaims.

ANSWER: Plaintiffs incorporate by reference their answer to paragraphs 101-106 from above.

117. Bristol-Myers repeats and realleges each of the allegations of paragraphs 23-89 above.

ANSWER: Plaintiffs respond to the allegations of paragraphs 23-89 of Defendant's Amended Answer starting with paragraph 23 below:

23. On August 17, 2000, Plaintiffs Repligen and the Regents of the University Of Michigan, sued Bristol-Myers in the Eastern District of Michigan, in an action styled The University of Michigan and Repligen Corporation v. Bristol-Myers Squibb Co. and identified as Civil Action No. 00-CV-73690 (The "Michigan Litigation").

ANSWER: Plaintiffs admit the allegations in paragraph 23 and also refer to Civil Action No. 00-CV-73690 in the Eastern District of Michigan as the "Michigan Litigation."

24. In the Michigan Litigation, Repligen and the University of Michigan asserted that Craig Thompson was either a sole and/or a co-inventor of United States Patent Nos. 5,434,131 ("the '131 patent"), 5,844,095 ("the '095 patent"), 5,851,795 ("the '795 patent"), 5,885,579 ("the '579 patent"), 5,968,510 ("the '510 patent"), 5,977,318 ("the '318 patent"), and 5,885,796 ("the '796 patent"), which claimed, inter alia, the compound CTLA4-Ig and its use as an immunosuppressant.

ANSWER: Referring to paragraph 24 of Defendant's Amended Answer, Plaintiffs admit only that, in the Michigan Litigation, Plaintiffs asserted that Dr. Craig B. Thompson was either a sole inventor or a joint inventor of United States Patent Nos. 5,434,131 ("the '131 patent"), 5,844,095 ("the '095 patent"), 5,851,795 ("the '795 patent"), 5,885,579 ("the '579 patent"), 5,968,510 ("the '510 patent"), 5,977,318 ("the '318 patent"), and 5,885,796 ("the '796 patent"). Plaintiffs deny the remaining allegations of paragraph 24.

25. Trial in the Michigan Litigation was held in April and May 2003 before the Honorable George Caram Steeh. Craig Thompson testified in that trial as a witness for Repligen and the University of Michigan.

ANSWER: Plaintiffs admit the allegations in paragraph 25.

26. Judge Steeh heard both fact and expert evidence on what CTLA4-Ig is, how it functions to regulate and suppress the immune system and its use to block T-cell and B-cell interactions.

ANSWER: Referring to paragraph 26, Plaintiffs admit only that Judge Steeh heard both the fact and expert evidence that is of record in the Michigan Litigation. Plaintiffs deny any remaining allegations of paragraph 26.

27. On September 10, 2003, Judge Steeh issued his twenty-seven page detailed decision, reported at 301 F.Supp.2d 633, in which he made the following findings, among others:

i. It was Bristol-Myers scientists, not Craig Thompson, who discovered that B7 was a natural ligand for CD28 and CTLA4.

ii. It was Bristol-Myers scientists, not Craig Thompson, who were the first to make a functional CTLA-4Ig fusion protein.

iii. It was Bristol-Myers scientists, not Craig Thompson, who were the first to determine that a functional CTLA-4Ig fusion protein bound a naturally-occurring ligand known as B7 with much higher affinity (binding strength) than did CD28, which is a surface protein present on T-cells.

iv. It was Bristol-Myers scientists, not Craig Thompson, who were the first to determine that a functional CTLA-4Ig fusion protein could be used to regulate T-cell interactions.

ANSWER: Referring to paragraph 27, Plaintiffs admit only that Judge Steeh issued "Findings of Fact and Conclusions of Law" dated September 10, 2003 and published at 301 F.Supp. 2d 633 ("the Michigan Opinion"). Plaintiffs deny any remaining allegations of paragraph 27.

28. Judge Steeh found that the Bristol-Myers scientists were the only inventors of, inter alia, the following patent claims, and that Craig Thompson had not made any inventive contribution to any of those inventions:

i. Claim 1 of the '131 patent: A method for regulating functional CTLA4 positive T cell interactions with B7 positive cells comprising contacting said B7 positive cells with a B7 ligand to interfere with reaction of B7 antigen with CTLA4, wherein said B7 ligand is a fusion protein that contains a portion of the extracellular domain of CTLA4, which portion binds B7.

ii. Claim 5 of the '131 patent: A method for treating immune system diseases mediated by T cell interactions with B7 positive cells comprising administering to a subject a B7 ligand to regulate T cell interactions with said B7 positive cells wherein said B7 ligand is a fusion protein that contains a portion of the extracellular domain of CTLA4, which portion binds B7. Claim 6 of the '131 patent: The method of claim 5, wherein said ligand is CTLA4Ig fusion protein.

iii. Claim 1 of the '579 patent: A method for regulating functional CTLA4 positive T cell interactions with B7 positive cells comprising contacting the B7 positive cells with a ligand for the B7 antigen, in a amount effective to interfere with reaction of endogenous B7 antigen with CTLA4, wherein the ligand is a soluble CTLA4 molecule.

iv. Claim 4 of the '579 patent: A method for treating immune system diseases mediated by T cell interactions with B7 positive cells comprising administering to a subject a ligand for B7 antigen, in an amount effective to regulate T cell interactions with said B7 positive cells.

ANSWER: Referring to paragraph 28, Plaintiffs admit only that Judge Steeh issued the Michigan Opinion. Plaintiffs deny any remaining allegations of paragraph 28.

29. Repligen and the University of Michigan appealed Judge Steeh's decision to the Court of Appeals for the Federal Circuit. That court heard argument on July 9, 2004 and summarily affirmed Judge Steeh on July 12, 2004. That decision is now final.

ANSWER: Referring to paragraph 29, Plaintiffs admit only that they appealed Judge Steeh's decision in the Michigan Litigation, that arguments were heard on July 9, 2004, and that the decision was affirmed without opinion on July 12, 2004. Plaintiffs deny any remaining allegations of paragraph 29.

30. As a result of the Michigan Litigation, it has been conclusively determined that Bristol-Myers scientists, and not any person from whom Repligen or the University of Michigan can claim rights, are the true and prior inventors of CTLA4-Ig and its use to regulate B-cell and T-cell mediated immune responses.

ANSWER: Plaintiffs deny the allegations of paragraph 30.

31. Repligen, the University of Michigan, and Bristol-Myers are the same entities that were parties in the Michigan Litigation.

ANSWER: Plaintiffs admit the allegations of paragraph 31.

32. Repligen and the University of Michigan had a full and fair opportunity to litigate the issues in the Michigan Litigation.

ANSWER: Referring to paragraph 32, Plaintiffs cannot meaningfully respond because Defendant's Amended Answer fails to define "the issues." Accordingly, Plaintiffs deny the allegations of paragraph 32.

33. Repligen and the University of Michigan are collaterally estopped from relitigating the fact findings made by Judge Steeh in his decision in the Michigan Litigation, attached hereto as Exhibit A.

ANSWER: Plaintiffs deny the allegations of paragraph 33.

34. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 102.

ANSWER: Plaintiffs deny the allegations of paragraph 34.

35. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 103.

ANSWER: Plaintiffs deny the allegations of paragraph 35.

36. Each and every claim of the '941 patent is invalid under 35 U.S.C. § 112.

ANSWER: Plaintiffs deny the allegations of paragraph 36.

37. The '941 patent fails to meet, and each claim of the '941 patent fails to meet, oneor more conditions of patentability specified in Part II of Title 35 of the United States Code.

ANSWER: Plaintiffs deny the allegations of paragraph 37.

38. Each and every claim of the '941 patent is unenforceable as a result of inequitable conduct during the prosecution of the '941 patent.

ANSWER: Plaintiffs deny the allegations of paragraph 38.

39. Each individual associated with the filing or prosecution of a patent application, including attorneys, has a duty of candor and good faith in dealing with the Patent Office. An individual breaches that duty when, with an intent to deceive the patent examiner, the individual fails to disclose to the Patent Office all information known to be material to the patentability of the claimed invention or misstates material information. A breach of a patent applicant's duty of candor renders unenforceable all claims which eventually issue from the application in connection with which such breach occurred and all claims that issue from any related applications.

ANSWER: Paragraph 39 does not include any allegations of fact, but rather reflects Bristol-Myers' characterization of the law of patent enforceability. Accordingly, Plaintiffs deny the allegations of paragraph 39.

40. All claims of the '941 patent are unenforceable because one or more individuals associated with the filing and/or prosecution of the '941 patent ("Applicants") committed inequitable conduct during the prosecution of the '941 patent.

ANSWER: Plaintiffs deny the allegations of paragraph 40.

41. Bristol-Myers realleges the allegations of paragraphs 23-33 above.

ANSWER: Plaintiffs incorporate by reference their answer to paragraphs 23-33 above.

42. Applicants knew of, but withheld from the Patent Examiner that Judge Steeh had decided the Michigan Litigation adversely to them and had rejected their claim that Craig Thompson was an inventor of CTLA4-Ig and its use to regulate immune responses.

ANSWER: Referring to paragraph 42, Plaintiffs admit only that Judge Steeh issued the Michigan Opinion and that the Applicants knew of the Michigan Opinion, but otherwise deny the allegations of paragraph 42.

43. The fact that Bristol-Myers, and not any person from whom Repligen or the University of Michigan claims rights, made those inventions, was material to the prosecution of the '941 patent, and Applicants withheld that information from the Patent Examiner with the intent to deceive.

ANSWER: Plaintiffs deny the allegations of paragraph 43.

44. Applicants also knew, and withheld from the Patent Office, the facts that the inventors named in the '941 patent had obtained and used information obtained from Bristol-Myers on CTLA4-Ig, its properties, and its use in regulating immune responses. On information and belief, information that Applicants obtained from Bristol-Myers and about Bristol-Myers' activities relating to CTLA4-Ig was at least part of their motivation to insert claims to the treatment of autoimmune diseases in the applications that led to the '941 patent.

ANSWER: Plaintiffs deny the allegations of paragraph 44.

45. Applicants also committed inequitable conduct by failing to disclose material prior art references to the Patent Office during the prosecution of the '941 patent, including Peter S. Linsley, et al., *Immunosuppression In Vivo by a Soluble Form of the CTLA-4 T Cell Activation Molecule*, 257 SCIENCE 792 (Aug. 7, 1992) ("Linsley article") and Deborah J. Lenschow, et al., *Long-Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4-Ig*, 257 SCIENCE 789 (Aug. 7, 1992) ("Lenschow article"). At least one of the individuals associated with the filing or prosecution of the '941 patent knew of these prior art references and of their materiality during the prosecution of the '941 patent but did not disclose them to the Patent Office, as set forth below.

ANSWER: Referring to paragraph 45, Plaintiffs admit only that at some point during the prosecution of the '941 patent at least one of the individuals associated with the filing or prosecution of the '941 patent was aware of the Linsley article (Linsley, et al., "Immunosuppression in Vivo by a Soluble form of the CTLA-4 T Cell Activation Molecule," *Science* 257:792-795) and Lenschow article (Lenschow, et al., "Long-Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4-Ig," *Science* 257:789-792). Plaintiffs deny the remaining allegations in paragraph 45.

46. In August 1992, the Linsley and Lenschow articles were both published in Science.

ANSWER: Referring to paragraph 46, Plaintiffs admit that the Linsley and Lenschow articles indicate on their face that they were published in August 1992 in *Science*. Plaintiffs deny the remaining allegations in paragraph 46.

47. The Linsley article discloses in vivo testing in which CTLA4-Ig was effective as an immunosuppressant.

ANSWER: Referring to paragraph 47, Plaintiffs admit that the Linsley article includes in its abstract the statement that "CTLA4Ig treatment in vivo suppressed T cell-dependent antibody responses to sheep erythrocytes or keyhole limpet hemocyanin" and presents experimental data purporting to support that statement, but otherwise deny the allegations of paragraph 47.

48. The Lenschow article also discloses in vivo testing in which CTLA4-Ig was effective as an immunosuppressant.

ANSWER: Referring to paragraph 48, Plaintiffs admit that the Lenschow article includes in its abstract the statement that "CTLA4Ig therapy blocked human pancreatic islet rejection in mice by directly affecting T cell recognition of B7+ antigen-presenting cells" and presents experimental data purporting to support that statement, but otherwise deny the allegations of paragraph 48.

49. In November 1992, an article entitled "T-cell activation by the CD28 ligand B7 is required for cardiac allograft rejection in vivo" was published in the Proceedings of the National Academy of Sciences. Laurence A. Turka, et al., 89 PROC. NAT'L ACAD. SCI. 11102 (Nov. 1992). This article was co-authored by Craig Thompson – one of the inventors named in the '941 patent – and cites both the Linsley and Lenschow articles.

ANSWER: Plaintiffs admit the allegations of paragraph 49.

50. On information and belief, Craig Thompson had access to, and knew of the existence and content of the Linsley and Lenschow articles before those articles were submitted to Science for publication. Because those articles were cited in the Turka et al. article, Craig Thompson knew of them by at least November 1992.

ANSWER: Plaintiffs are without sufficient information to admit or deny the allegations of paragraph 50, and therefore deny the same.

51. On November 10, 1994, Repligen filed United States Patent Application No. 08/337,960 ("the '960 application"). The PCT Application corresponding to the '960 application (International Publication No. WO96/14865), was published and its specification cites the Lenschow article.

ANSWER: Plaintiffs admit the allegations of paragraph 51.

52. On February 2, 1996, Repligen filed another patent application that led to U.S. Patent No. 6,444,792 (the "Repligen '792 patent"). The specification of the Repligen '792 patent refers to the Linsley article.

ANSWER: Plaintiffs admit the allegations of paragraph 52.

53. The Lenschow article was cited on the face of the Repligen '792 patent during the pendency of the '941 patent before the Patent Office.

ANSWER: Plaintiffs admit the allegations of paragraph 53.

54. Individuals employed by Repligen who were associated with the filing and/or prosecution of the '941 patent knew of the Linsley and Lenschow articles by at least February 2, 1996.

ANSWER: Plaintiffs admit the allegations of paragraph 54.

55. On September 25, 1996, the Patent Examiner of the '941 patent rejected pending claims of the application as being anticipated by the '131 patent, assigned to Bristol-Myers. The rejected claims were directed to a method of treating a patient having an autoimmune disease by administering "a ligand which binds a naturally occurring CD28 stimulatory ligand." A rejected dependent claim specified that the ligand was CTLA4-Ig.

ANSWER: Referring to paragraph 55, Plaintiffs admit that on September 25, 1996, the Examiner of the '941 patent rejected claims 25-30 of the application that matured into the '941 patent as being anticipated by the '131 patent under 35 U.S.C. § 102(e). At this time, claim 25 referred to "a method of treating a patient having an autoimmune disease comprising administering to the patient a ligand which binds a naturally occurring CD28 stimulatory ligand in an amount effective to suppress the patient's immune response." Claim 28 indicated that "the ligand comprises CTLA4-Ig." Plaintiffs deny any remaining allegations.

56. In response to the rejection, on March 25, 1997, Applicants cancelled all of the claims that referred to CTLA4-Ig and amended the remaining claims to limit them to the use of "a fragment of an anti-CD28 antibody" instead of the use of "a ligand which binds a naturally occurring CD28 stimulatory ligand." As a result of that amendment, the application no longer contained claims to the use of CTLA4-Ig for the treatment of any autoimmune disease.

ANSWER: Referring to paragraph 56, Plaintiffs admit only that certain claims were cancelled and that, at the time of the March 25, 1997 cancellation and Amendment, the application no longer contained claims to the use of CTLA4-Ig for the treatment of any autoimmune disease. Plaintiffs deny any remaining allegations.

57. After about four more years of prosecution, on June 4, 2001, Applicants added back claims that eventually issued as the claims of the '941 patent directed to methods of CTLA4-Ig. In the amendment, Applicants told the Patent Examiner that the '131 patent merely demonstrates that CTLA-4Ig is an inhibitor of *in vitro* immune responses dependent upon cellular interactions and suggests *in vivo* applications for immune system diseases. [The '131 patent] clearly does not teach or enable methods for treating MS, SLE, RA and scleroderma by administering CTLA-4Ig. In fact, [the '131patent] doesn't even mention these diseases. Moreover, at column 25, lines 6-11, [the '131 patent] states:

> "The immunosuppressive effects of CTLA4-Ig *in vitro* suggest that ***future investigations are warranted*** into possible therapeutic effects of this molecule for treatment of autoimmune disorders involving aberrant T cell activation or Ig production." (emphasis added)

[The '131 patent] therefore actually admits that it does not enable the presently claimed methods.

ANSWER: Referring to paragraph 57, Plaintiffs admit that the Amendment and Response dated June 4, 2001 included claims that eventually issued as some of the claims of the '941 patent. Plaintiffs admit that paragraph 57 includes a quotation from the Amendment and Response dated June 4, 2001, in which text referring to "Linsley et al." has been substituted with "[the '131 patent]." Plaintiffs deny any remaining allegations.

58. Applicants withheld the Linsley and Lenschow articles from the Patent Office. The Linsley and Lenschow articles are each material and not cumulative because each discloses *in vivo* data to show the immunosuppressive effects of CTLA4-Ig. The Linsley article states at page 794:

> We demonstrated that CTLA4Ig is a potent immunosuppressive agent in vivo, in agreement with previous in vitro results...Our data suggest that CTLA4Ig has attractive features for an immunosuppressive drug (that is, in vivo stability, low toxicity, and high specificity)...Our results showing that

> CTLA4Ig also suppressed humoral response suggest potential uses of CTLA4Ig in the treatment of Ab-mediated autoimmune diseases.

In addition, the Lenschow article states at page 792:

> The capacity of CTLA4Ig to significantly prolong human islet graft survival in mice in a donor-specific manner suggests that blocking the interaction of costimulatory molecules such as CD28-B7 may provide an approach to immunosuppression.

ANSWER: Referring to paragraph 58, Plaintiffs admit only that this paragraph quotes the Linsley and Lenschow articles, but deny the remaining allegations in paragraph 58.

59. Applicants argued to the Patent Office that there was a lack of *in vivo* prior art data demonstrating the immunosuppressive effects of CTLA4-Ig when they were fully aware of the existence of the Linsley and Lenschow articles, which supplied that information, as well as the relationship between the *in vivo* data and the use of CTLA4-Ig for the treatment of autoimmune diseases.

ANSWER: Referring to paragraph 59, Plaintiffs admit only that Plaintiffs made the statement quoted in paragraph 57 of Defendant's Amended Answer, but otherwise deny the allegations of paragraph 59.

60. Applicants withheld the Linsley and Lenschow articles with an intent to mislead the Patent Office. By failing to disclose the Linsley and Lenschow articles, Applicants misled the Patent Examiner regarding the disclosure of *in vivo* testing which demonstrated the immunosuppressive effects of CTLA4-Ig and its use to treat autoimmune diseases in the prior art.

ANSWER: Plaintiffs deny the allegations of paragraph 60.

61. Applicants committed inequitable conduct by failing to disclose to the Patent Examiner testimony by Craig Thompson, as well as Damle et al., *Direct helper T-cell-induced B cell differentiation involves interaction between T cell antigen CD28 and B cell activation antigen B7*, 21 EURO. J. IMMUNOL. 1277 (1991) ("Damle").

ANSWER: Plaintiffs deny the allegations of paragraph 61.

62. Applicants' statement in their June 4, 2001 amendment (quoted above) that the '131 patent "does not even mention these diseases" was misleading, because Applicants knew that persons of ordinary skill in the art were aware that multiple

sclerosis and rheumatoid arthritis were commonly known to be autoimmune diseases.

ANSWER: Plaintiffs deny the allegations of paragraph 62.

63. Craig Thompson testified under oath in the Michigan Litigation that:

> Q. And one of the examples of autoimmune diseases that you gave ways [sic] rheumatoid arthritis?
>
> A. Yes.
>
> Q. And would other examples of autoimmune diseases would be things like multiple sclerosis or organ transplant complications?
>
> A. Yes.
>
> Q. And for [sic] all those things known to be autoimmune diseases in the 1990 time frame?
>
> A. I believe most people believe there [sic] were autoimmune diseases during that time, yes.

Thompson Tr., May 1, 2003, page 1, line 17 - page 2, line 2.

ANSWER: Plaintiffs admit the allegations of paragraph 63.

64. On information and belief, Applicants were aware that Damle specifically identified rheumatoid arthritis and systemic lupus erythematosis ("SLE") as autoimmune diseases that could be treated by regulating CD28/B7 interactions using molecules that target CD28 and B7.

ANSWER: Plaintiffs are without sufficient information to admit or deny the allegations of paragraph 64, and therefore deny the same.

65. The '131 patent and the Linsley article disclosed that CTLA4-Ig targeted B7.

ANSWER: Referring to paragraph 65, Plaintiffs cannot meaningfully respond because Defendants' Amended Answer fails to define "targeted." Plaintiffs admit only that the Linsley article and the '131 patent include statements that CTLA-4Ig binds to B7, but deny the remaining allegations of paragraph 65.

66. The Thompson testimony and Damle article were material because each evidences that a person of ordinary skill in the art would have understood that rheumatoid arthritis and SLE were examples of the autoimmune diseases referred to in the '131 patent, which the Patent Examiner had relied on to reject the claims, and which Applicants distinguished by arguing that it did not identify any autoimmune disease.

ANSWER: Plaintiffs deny the allegations of paragraph 66.

67. On information and belief, Applicants' failure to disclose the Thompson testimony and the Damle reference were made with the intent to mislead the Patent Office regarding the scope of the teaching in the '131 patent.

ANSWER: Plaintiffs deny the allegations of paragraph 67.

68. On information and belief, Applicants were aware that statements in their specification and statements made to the Patent Office about Example XVI of the '941 patent were unfounded, false and misleading.

ANSWER: Plaintiffs deny the allegations of paragraph 68.

69. Applicants made the following representations to the Patent Office regarding the predictive ability of the EAE model of Example XVI in treating autoimmune disease in humans: (i) Applicants represented in their '941 patent specification that:

> "Experimental Autoimmune Encephalomyelitis (EAE) is a rodent and primate model for multiple sclerosis." (column 47, lines 66-67). "As shown in FIG. 22, mice receiving huCTLA-4Ig-treated cells (designated PPIB CTLA-4) showed a significantly reduced severity of their first episode of disease as compared to mice receiving untreated cells (designated PPIA control). In addition, ensuing relapses in the mice receiving huCTLA-4Ig-treated cells were less severe than in mice receiving cells not exposed to huCTLA-4Ig. In fact, all five mice receiving huCTLA-4Ig-treated cells stopped relapsing, and no longer showed signs of disease at 80-100 days post transfer." (column 48, lines 31-41).
>
> "Clinical disease severity was reduced even further by treating both the donor mice and the cultured cells with huCTLA-4Ig (FIG. 23)." (column 48, lines 42-44).
>
> "Treatment of either the donor mice or the in vitro cultures resulted in significantly reduced clinical disease severity. Treatment of both the donor mice and the cultured cells with huCTLA-4Ig was the most effective protocol for reducing clinical disease severity." (column 48, lines 51-55).

"Direct administration of huCTLA-4Ig to mice receiving adoptively transferred cells was also examined. As shown in FIG. 24, when PLSJLFI/J recipient. mice were given 100 µg of either huCTLA-4Ig or human IgG in PBS intraperitoneally on days 1 to 9 post transfer, no difference in disease severity was observed between the two groups of mice. However, in experiments utilizing SJL/J mice, reduced disease severity during relapse was noted in mice treated with 100 µg huCTLA-4Ig intraperitoneally on days 1 to 5 post transfer (FIG. 25)." (column 48, lines 56-65).

"Administration of huCTLA-4Ig markedly reduced the mean clinical severity of disease in these animals, as compared to the mice treated with IgG1. These findings indicate that direct administration of soluble human huCTLA-4Ig can provide an effective therapeutic strategy in the treatment of autoimmune disease." (column 49, lines 34-39).

(ii) Applicants represented to the Patent Office:

On May 19, 1994 that: "Further, Applicants' specification shows that autoimmune disease can be treated in a subject by administering to the subject a selected inhibitory ligand that binds a natural stimulatory ligand to CD28. See, Specific Example XVI and Figs. 22-27, showing for example in an accepted in vivo murine model for the autoimmune disease multiple sclerosis that the clinical severity of the disease state can be reduced by administration of a soluble CTLA-4 (huCTLA-4Ig).

The examples in Applicants' specification employ model systems that are acceptable, in view of Applicants' disclosure taken as a whole, as being reasonably predictive of having the state utility."

On November 21, 1995 that: Example XVI provides one basis of support for the addition of the new claims. Claim 25 is a representative claim as follows: A method of treating a patient having an autoimmune disease comprising administering to the patient a ligand which binds a naturally occurring CD28 stimulatory ligand in an amount effective to suppress the patient's immune response.

On August 7, 1998 and May 6, 1999 that: "Applicants also refer the Examiner to Specific Example XVI of the present specification, describing the efficacy of CTLA4-Ig in an adoptively transferred EAE and direct EAE murine model. Although these studies employ CTLA4-Ig, due to the essential nature of CD28 in the stimulatory pathway, one skilled in the art after learning of the primate study and the murine EAE model studies, and in light of the superantigen murine model studies, could heuristically conclude that the claimed methods utilizing anti-CD28 antibody fragments would be effective in treating autoimmune disease in humans."

> On June 4, 2001 that: "Applicants submit that one skilled in the art, after reading the specification, would be able to make and use the now claimed invention. In particular, Applicants refer the Examiner to Specific Example XVI which describes the effective use of CTLA-4Ig in an adoptively transferred EAE and direct EAE murine model. As discussed at the interview, Applicants specifically draw the Examiner's attention to Figure 27 which shows that in a direct (active) model of EAE, CTLA-4Ig is not only effective at reducing the mean clinical severity at the onset of disease (e.g. days 10-25), but is extremely effective in reducing the mean clinical severity of disease when disease is ongoing (e.g. days 25-45)."

ANSWER: Plaintiffs admit only that the quoted passages are taken from the prosecution of the '941 patent, but deny the remaining allegations of paragraph 69.

70. Applicants knew those statements were false and that the EAE model did not accurately reflect a human therapeutic situation.

ANSWER: Plaintiffs deny the allegations of paragraph 70.

71. The claims of the '941 patent are directed to treating autoimmune diseases, specifically rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosis and scleroderma in patients.

ANSWER: Referring to paragraph 71, Plaintiffs admit that the claims of the '941 patent are directed at least to treating rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosis and scleroderma in patients. Plaintiffs deny the remaining allegations of paragraph 71.

72. Contrary to the affirmative representations that Applicants made in the specification and in their arguments to the Patent Examiner, Applicants knew that their EAE data did not show any significant efficacy in reducing either the progression or the severity of the experimental disease.

ANSWER: Plaintiffs deny the allegations of paragraph 72.

73. On information and belief, Applicants knew, but did not tell the Patent Examiner, that the EAE test of Example XVI was (a) not a predictor of efficacy in treating multiple sclerosis in humans and (b) not a predictor of efficacy in treating any of the other autoimmune diseases recited in the claims of the '941 patent, and specifically not a predictor of efficacy in treating rheumatoid arthritis.

ANSWER: Plaintiffs deny the allegations of paragraph 73.

74. The '941 patent contains no in vivo data and no in vivo animal models that are indicators of efficacy in treating rheumatoid arthritis.

ANSWER: Plaintiffs deny the allegations of paragraph 74.

75. Applicants knew those material misstatements were relevant to the review of their patent application by the Patent Office because their claims had been rejected as not enabled in Official Actions dated August 7, 1997, November 6, 1998, December 2, 2000, and January 15, 2002. On information and belief Applicants' misstatements were made with intent to mislead the Patent Office concerning the ability of the EAE model to predict treatment for human diseases when in fact the EAE model does not predict treatment for any human disease.

ANSWER: Plaintiffs deny the allegations of paragraph 75.

76. Each and every claim of the '941 patent is unenforceable as a result of Applicants deceptively failing to name the proper inventors.

ANSWER: Plaintiffs deny the allegations of paragraph 76.

77. On February 17, 1992, Dr. Laurence Turka and Dr. Craig Thompson of Plaintiff University of Michigan submitted a research proposal to Bristol-Myers to perform *in vivo* cardiac allograft experiments using CTLA4-Ig supplied by Bristol-Myers ("Research Proposal", Exhibit B).

ANSWER: Plaintiffs admit only that Drs. Turka and Thompson sent Dr. Peter Linsley a letter and research proposal dated February 17, 1992, but bearing a facsimile transmission date of February 20, 1992. Plaintiffs deny the remaining allegations.

78. The Research Proposal included the following work, to be performed by the University of Michigan:

i. Determining the optimal means of administering CTLA4-Ig, in part, by administering CTLA4-Ig at less than 500 µg/day for seven days.

ii. Defining the immunologic mechanism by which CTLA4-Ig prevents allograft rejection, in part, by performing thymectomies on animals prior to transplantation.

ANSWER: Plaintiffs admit only that the "Research Proposal" includes the following quotations:

> As previously presented, our preliminary experiments in an experimental animal model (rat cardiac allograft transplantation)

> indicate that CTLA-4Ig is a potent immunosuppressive agent with significant potential for clinical use in organ transplantation. We propose to extend our initial work with CTLA-4Ig:
> 1. Determine the optimal means to administer CTLA-4Ig, including dose and duration of therapy. . . . .
> 2. Define the immunologic mechanism by which CTLA-4Ig prevents allograft rejection.

(page 2) and

> Therefore, the first set of experiments will determine the lowest effective dose of CTLA4-Ig. We would anticipate initially testing doses from 25-250 μg/day for 7 consecutive days.

(page 3) and

> Host animals will undergo thymectomy prior to transplantation.

(page 5). Plaintiffs deny any remaining allegations of paragraph 78.

79. Under the Research Proposal, it was understood that Bristol-Myers would supply the CTLA4-Ig used in the work.

ANSWER: Plaintiffs deny that the "Research Proposal" specified that Bristol-Myers would supply CTLA4-Ig. Plaintiffs are unable to respond to any remaining allegations because paragraph 79 is unclear as to whose understanding is being referred to. Accordingly, Plaintiffs deny the remaining allegations of paragraph 79.

80. Upon information and belief, the work identified above in paragraph 78 went forward in good faith before a formal agreement was executed.

ANSWER: Plaintiffs deny that paragraph 78 of Defendant's Amended Answer refers to any work before a formal agreement was executed and accordingly deny the allegations of paragraph 80.

81. The Research Proposal was formalized into an agreement dated April 16, 1992 ("Research Agreement", Exhibit C).

ANSWER: Plaintiffs admit that the "Research Agreement" includes parts of the "Research Proposal," but deny the remaining allegations of paragraph 81.

82. Under the Research Agreement, Bristol-Myers and the University of Michigan agreed to collaborate in research related to CTLA4-Ig. (Exhibit C at 1).

ANSWER: Plaintiffs admit only that the "Research Agreement" states that Bristol-Myers "is interested in collaborating." Plaintiffs deny the remaining allegations of paragraph 82.

83. Under the Research Agreement, Bristol-Myers agreed to fund the University of Michigan to perform in vivo cardiac allograft experiments. (Exhibit C at ¶ 5).

ANSWER: Plaintiffs admit that the "Research Agreement" at ¶ 5 states that Bristol-Myers "will provide funding in the amounts of $28,856 and $20,289" for certain *in vivo* cardiac allograft experiments. Plaintiffs deny the remaining allegations of paragraph 83.

84. Upon information and belief, Dr. Turka performed the in vivo cardiac allograft experiments that were the subject of the Research Proposal and Research Agreement.

ANSWER: Plaintiffs admit only that Dr. Turka was involved in performing *in vivo* cardiac allograft experiments with CTLA4-Ig. Plaintiffs are currently without sufficient information to determine what experiments, if any, were the subject of the Research Proposal and Research Agreement, and accordingly deny the remaining allegations of paragraph 84.

85. While Dr. Thompson was originally named in the Research Agreement as a project director in the paragraph entitled "Key Personnel", his name was crossed off. (Exhibit C at ¶ 3).

ANSWER: Plaintiffs admit only that Dr. Thompson's name appears in the agreement as a "project director" in the paragraph entitled "Key Personnel," and further admit that Dr. Thompson's name is crossed off. Plaintiffs are without sufficient information to respond to the remaining allegations, and therefore deny the same.

86. The work performed pursuant to the Research Proposal is disclosed and relied on in the '941 patent, in Example X.

ANSWER: Plaintiffs deny the allegations of paragraph 86.

87. The Applicants relied on Example X during prosecution of the '941 patent. For example:

> Applicant submits that the pending claims are fully enabled and one skilled in the art would be able to make and use the claimed invention without undue experimentation. At the outset, Applicant incorporates herein the arguments set forth in the prior responses.
> (July 19, 2002 After Final Response Under 37 C.F.R. §1.116 at 2).
>
> Applicants have added new Claims 39-48. Support for the new claims may be found throughout the application and in particular, without limitation, . . . Specific Examples X and XVI.
> (May 10, 1999 Amendment and Response at 3).
>
> Applicants have cancelled Claims 1-24 and have added new Claims 25-34. Bases for the new claims may be found throughout the application as filed and in particular, without limitation, . . . Specific Examples X and XVI.
> (November 21, 1995 Preliminary Amendment at Remarks).

ANSWER: Plaintiffs admit that the Applicants referred to Example X as quoted above from the prosecution history of the '941 patent, but deny any further implications from these statements.

88. Upon information and belief, Dr. Turka performed the in vivo cardiac experiments identified above in paragraph 78 that are disclosed in and relied on in the '941 patent.

ANSWER: As stated in the answer to Paragraph 86, Plaintiffs deny that the experiments identified in paragraph 78 are disclosed in and relied on in the '941 patent. The answer to paragraph 84 responds to Defendant's allegation that Dr. Turka performed the *in vivo* cardiac allograft experiments that were the subject of the Research Proposal and Research Agreement. Plaintiffs deny the remaining allegations of paragraph 88.

89. Upon information and belief, Applicants did not name Dr. Turka as an inventor on the '941 patent with deceptive intent.

ANSWER: Plaintiffs deny the allegations of paragraph 89.

118. An actual controversy exists between Bristol-Myers and Plaintiffs over the alleged enforceability of the '941 patent.

ANSWER: Plaintiffs admit the allegations of paragraph 118.

119. Each and every claim of the '941 patent is unenforceable as a result of inequitable conduct during the prosecution of the '941 patent. The inequitable conduct is detailed in paragraphs 38-89 above.

ANSWER: Plaintiffs deny the allegations of paragraph 119 and incorporate by reference their answer to paragraphs 38-89 above.

COUNT IV

DECLARATORY JUDGMENT THAT BRISTOL-MYERS HAS A ROYALTY-FREE LICENSE TO PRACTICE THE '941 PATENT AND A RIGHT OF OWNERSHIP TO THE'941 PATENT

120. Bristol-Myers incorporates by reference the allegations made in paragraphs 101-106, above, of Bristol-Myers' Counterclaims.

ANSWER: Plaintiffs incorporate by reference their answer to Paragraphs 101-106 above.

121. Bristol-Myers repeats and realleges each of the allegations of paragraphs 77-88, 93-95 and 98-99 above.

ANSWER: Plaintiffs incorporate by reference their answer to Paragraphs 77-88 above. Paragraphs 93-94 and 98-99 are answered below.

93. The Research Agreement was signed on behalf of the University of Michigan by Paul J. Stemple (Manager, Office of Contract Administration) and was acknowledged by University of Michigan personnel Dr. Turka, Dr. Hua Lin, and Dr. Steven Bolling. (Exhibit C at 4). The Research Agreement was signed on behalf of Bristol-Myers by Ingegerd Hellstrom, Vice President Exploratory Biomedical Research. (Id.).

ANSWER: Plaintiffs admit only that the "Research Agreement" was signed by Paul J. Stemple, Laurence Turka, Hua Lin, Steven Bolling, and Ingegerd Hellström, but deny the remaining allegations of paragraph 93.

94. The Research Agreement granted Bristol-Myers a royalty-free license to each useful discovery resulting from the research program between Bristol-Myers and the University of Michigan:

> Invention Rights:
>
> A. Any and all data, samples, discoveries, inventions, improvements, trade secrets and the like, whether patentable or unpatentable, conceived or made by [University of Michigan] emanating from or relating to [University of Michigan's] services and [Bristol-Myers'] materials under this Agreement, shall be the joint property of the parties. In consideration of [Bristol-Myers'] contributions to the research program, [University of Michigan] hereby grants to [Bristol-Myers] a non-exclusive worldwide royalty-free license to each useful discovery, whether patentable or unpatentable.

(Exhibit C at ¶ 7).

ANSWER**:** Plaintiffs admit only that the "Research Agreement" includes the Invention Rights section quoted in paragraph 94, but deny the remaining allegations of this paragraph.

95. If and to the extent the subject matter that is claimed in the '941 patent is a useful discovery, it falls within that grant.

ANSWER: Plaintiffs deny the allegations of paragraph 95.

98. The Research Agreement provides that any and all discoveries and inventions conceived or made by the University of Michigan emanating from or relating to the University of Michigan's services and Bristol-Myers' materials under the Research Agreement shall be the joint property of the parties.

ANSWER: Plaintiffs admit only that the "Research Agreement" includes the section quoted in paragraph 94 of Defendant's Amended Answer, but deny the remaining allegations of paragraph 98.

99. The claimed invention in the '941 patent emanated from and/or related to Bristol-Myers' materials under the Research Agreement.

ANSWER: Plaintiffs deny the allegations of paragraph 99.

122. Subject matter jurisdiction for this claim exists under 28 U.S.C. § 2201 and principles of pendent jurisdiction. There exists an actual controversy between Bristol-Myers and Plaintiffs with respect to Bristol-Myers' rights under the "Invention Rights" provision of the Research Agreement.

ANSWER: Plaintiffs admit the allegations of paragraph 122.

123. Bristol-Myers holds a royalty-free license under the '941 patent and is entitled to a declaration to that effect.

ANSWER: Plaintiffs deny the allegations of paragraph 123.

124. Bristol-Myers holds a right of ownership to the '941 patent and is entitled to a declaration to that effect.

ANSWER: Plaintiffs deny the allegations of paragraph 129.

COUNT V
BREACH OF CONTRACT

125. Bristol-Myers incorporates by reference the allegations made in paragraphs 101-106 and 122, above, of Bristol-Myers' Counterclaims.

ANSWER: Plaintiffs incorporate by reference their answer to Paragraphs 101-106 and 122 above.

126. Bristol-Myers repeats and realleges each of the allegations of paragraphs 77-88, 93-95, and 98-99 above.

ANSWER: Plaintiffs incorporate by reference their answer to Paragraphs 77-88, 93-95, 98-99 above.

127. The Research Agreement (see Exhibit C) is a binding and legally enforceable contract supported by adequate consideration.

ANSWER: Plaintiffs are without sufficient information to admit or deny the allegations of paragraph 127, and therefore deny the same.

128. Bristol-Myers has fully performed all of its obligations under the Research Agreement.

ANSWER: Plaintiffs are without sufficient information to admit or deny the remaining allegations of paragraph 128, and therefore deny the same.

129. Plaintiff University of Michigan has inexcusably and materially breached the Research Agreement by asserting the '941 patent against Bristol-Myers and participating in this litigation.

ANSWER: Plaintiffs deny the allegations of paragraph 129.

130. As a direct and proximate result of Plaintiff University of Michigan's breach of the Research Agreement, Bristol-Myers has suffered, and will suffer, damages.

ANSWER: Plaintiffs deny the allegations of paragraph 130.

131. As a result of Applicants' inequitable conduct and because Plaintiffs brought this suit knowing the '941 patent is invalid and unenforceable, this is an exceptional case such that Bristol-Myers is entitled to an award of its reasonable attorneys' fees, as provided by 35 U.S.C. §285.

ANSWER: Plaintiffs deny the allegations of paragraph 131.

132. Bristol-Myers demands trial by jury on all affirmative defenses, counterclaims, and issues triable by jury.

ANSWER: Plaintiffs admit only that the Defendant's Amended Answer includes a jury demand, but deny all other allegations in paragraph 132.

133. For the reasons set forth above, Bristol-Myers prays for the Court's judgment

(a) the '941 patent is invalid and each claim of the '941 patent is invalid;
(b) Bristol-Myers has not infringed any valid claim of the '941 patent;
(c) the '941 patent is not enforceable;
(d) Bristol-Myers has a royalty-free license under the '941 patent;
(e) Bristol-Myers is an owner of the '941 patent;
(f) Plaintiffs' Complaint be dismissed with prejudice;
(g) Plaintiffs take nothing by reason of their claims against Bristol-Myers;
(h) costs of this action be assessed against Plaintiffs;
(i) awards Bristol-Myers damages in an amount to be proved at trial;
(j) awards Bristol-Myers any and all pre-judgment and post-judgment interest to which it is entitled;
(k) awards Bristol-Myers its reasonable attorneys' fees; and
(l) awards Bristol-Myers such other and further relief at law or equity as the Court may deem just and proper.

ANSWER: Plaintiffs deny that Defendant Bristol Myers is entitled to any of the relief that it seeks.

Otherwise, Plaintiffs deny all allegations that are not expressly admitted above.

Respectfully submitted,

Dated: December 21, 2006

By: /s/ Sam Baxter

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CERTIFICATE OF SERVICE

The undersigned certifies that a true and correct copy of the foregoing documents was served on counsel of record via the Court's ECF system on December 21, 2006.

/s/ Sam Baxter

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

REPLIGEN CORPORATION AND THE REGENTS OF THE UNIVERSITY OF MICHIGAN,	§	
Plaintiffs,	§	Civil Action No. 2:06-CV-00004 (TJW)
v.	§	
BRISTOL-MYERS SQUIBB COMPANY,	§	
Defendant.	§	

CLAIM CONSTRUCTION ORDER

After considering the submissions and the arguments of counsel, the Court issues the following order concerning the claim construction issues:

The parties agree to the constructions listed below:

Claim Term	**Agreed Construction**
"A method of treating" (claim 3)	A method that can reasonably be expected to alleviate a patient's symptoms
"a patient having rheumatoid arthritis" (claim 3)	A patient who has rheumatoid arthritis, which is a specific autoimmune disease generally characterized by inflammation and stiffening of the joints.
"in an amount effective" (claim 3)	A quantity sufficient to achieve the desired result.
"immunosuppressant" (claim 7)	An agent that can suppress an immune response.

The Court determines that the following construction is appropriate for the sole term in dispute:

Claim Term	**Court's Construction**
"to suppress the immune response" (claim 3)	To down-modulate the immune response

The Court adopts the above listed constructions.

SIGNED this 2nd day of October, 2007.

CHARLES EVERINGHAM IV
UNITED STATES MAGISTRATE JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

REPLIGEN CORPORATION and THE REGENTS OF THE UNIVERSITY OF MICHIGAN, Plaintiffs, v. BRISTOL-MYERS SQUIBB COMPANY, Defendant.	Case No. 2:06-CV-004

JOINT MOTION FOR ENTRY OF STIPULATED ORDER OF DISMISSAL

Having fully resolved the claims asserted in this action, Plaintiffs Repligen Corporation and The Regents of the University of Michigan (collectively "Plaintiffs") and Defendant Bristol-Myers Squibb Company ("Bristol") jointly move the Court for entry of the attached Stipulated Order of Dismissal.

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing document was served on all parties via United States mail and/or electronic delivery this 9th day of April, 2008.

/s/ Wesley Hill
Wesley Hill

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

REPLIGEN CORPORATION and THE REGENTS OF THE UNIVERSITY OF MICHIGAN, Plaintiffs, v. BRISTOL-MYERS SQUIBB COMPANY, Defendant.	Case No. 2:06-CV-004

STIPULATED ORDER OF DISMISSAL

WHEREAS Plaintiffs Repligen Corporation and The Regents of the University of Michigan (collectively "Plaintiffs") and Defendant Bristol-Myers Squibb Company ("Bristol"), as indicated by the signature of counsel appearing below, have agreed to the dismissal of this action, pursuant to Federal Rule of Civil Procedure 41 and subject to the terms of this Order and a settlement agreement, dated April 7, 2008,

NOW, THEREFORE, it is ordered as follows:

1. The claims by Plaintiffs against Bristol are hereby dismissed with prejudice.

2. The claims by Bristol against Plaintiffs are hereby dismissed with prejudice.

3. Each party shall bear its own costs and attorneys fees attributable to the prosecution and defense of the claims.

STIPULATED AND AGREED

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SO ORDERED: