IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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| HUMAN GENOME SCIENCES, INC.,<br>Plaintiff,<br>v.<br>GENENTECH, INC., and CITY OF HOPE,<br>Defendants. | C.A. No. _____<br>**DEMAND FOR JURY TRIAL** |

## COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Human Genome Sciences, Inc. ("HGS"), by and through undersigned counsel, files this Complaint against Genentech, Inc. and City of Hope (collectively, "Defendants") and alleges as follows:

## NATURE OF THE CASE

1. HGS seeks a declaration that U.S. Patent No. 6,331,415 titled "Methods of Producing Immunoglobulins, Vectors and Transformed Host Cells for Use Therein" (the "Cabilly II Patent," attached as Exhibit A), including the *Ex Parte* Reexamination Certificate issued pursuant to Reexamination Nos. 90/007,542 and 90/007,859, is invalid, unenforceable and not infringed by the manufacture, use, importation, offer to sell or sale of HGS's Benlysta® (belimumab) antibody.

2. HGS has manufactured and is currently manufacturing Benlysta®, a recombinantly engineered monoclonal antibody which is being developed for the treatment of autoantibody-positive patients with systemic lupus erythematosus ("Lupus"). If approved, Benlysta® would be the first new approved drug for Lupus in more than fifty years.

3. HGS has expended substantial resources researching and developing Benlysta®, including filing a Biologic License Application ("BLA") with the United States Food and Drug Administration ("FDA"). HGS also has expended substantial resources in preparing to launch and commercialize Benlysta®.

4. In the near future, HGS expects a decision from the FDA regarding the approval of HGS's BLA for Benlysta®. Upon approval, HGS intends to market Benlysta® in this District.

5. Defendants have asserted that the Cabilly II Patent broadly covers the use of certain well-known, conventional recombinant methods to produce virtually any antibody product in any type of host cell. Defendants also have asserted multiple infringement claims under the Cabilly II Patent against companies who have made and sold antibody products that were produced using recombinant methods similar to the methods used by HGS to make Benlysta®. *See MedImmune Inc. v. Genentech, Inc.*, Case No. 03-cv-02567 (C.D. Cal.); *Centocor, Inc. v. Genentech, Inc.*, Case No. 08-cv-03573 (C.D. Cal.); *Glaxo Group Ltd. v. Genentech, Inc.*, Case No. 2:10-cv-02764 (C.D. Cal.).

6. In a pending action pertaining to a different antibody, Arzerra™, Defendants specifically averred that Benlysta® infringes Claims 18 and 20 of the Cabilly II Patent and that they "intend shortly" to assert infringement claims against HGS. See *Glaxo Group Ltd. v. Genentech, Inc.*, Case No. 2:10-cv-02764 (C.D. Cal.) (Genentech, Inc. and City of Hope's Opening Brief on Claim Construction dated Jan. 7, 2011), Dkt. No. 83 at FN4. Given Defendants' acts and statements and HGS's intended sale of Benlysta®, a real, immediate and substantial dispute exists between the parties concerning the Cabilly II Patent for which HGS now seeks declaratory relief.

## PARTIES

7. Plaintiff HGS is a corporation duly organized and existing under the laws of the State of Delaware, with its principal place of business at 14200 Shady Grove Road, Rockville, Maryland 20850.

8. Defendant Genentech, Inc. ("Genentech") is a corporation duly organized and existing under the laws of the State of Delaware, with its principal place of business in South San Francisco, California.

9. Defendant City of Hope is a not-for-profit organization duly organized and existing under the laws of the State of California, with its principal place of business in Duarte, California. On information and belief, City of Hope conducts business in the State of Delaware and has developed valuable relationships and generated goodwill through advertising and educational initiatives, including having a Regional Development Office serving Delaware at 1608 Walnut Street #1702, Philadelphia, Pennsylvania 19103. On information and belief, as part of its business efforts, City of Hope routinely invites businesses in Delaware to donate time and raise funds for its research and treatment programs.

10. On information and belief, Genentech and City of Hope are co-assignees of the Cabilly II Patent. On information and belief, City of Hope has an ongoing relationship with Genentech which involves dealings beyond simply receiving royalty income on the Cabilly II Patent, including coordinating patent prosecution and maintenance and the federal litigation of infringement claims (in which City of Hope and Genentech are represented jointly by counsel).

## JURISDICTION AND VENUE

11. This action arises under the Declaratory Judgment Act of 1934 (28 U.S.C. § 2201), Title 28 of the United States Code, for the purposes of determining an actual and justiciable controversy between the parties, and the patent laws of the United States, Title 35 of

the United States Code. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

12. This Court has personal jurisdiction over Genentech based on its incorporation and business in Delaware. On information and belief, this Court has personal jurisdiction over City of Hope based on its business activities in and directed to Delaware and its established and ongoing relationship with its co-assignee Genentech. Because of the multifaceted relationship between City of Hope and Genentech, including coordinating prosecution and maintenance of the Cabilly II Patent and control over federal litigation, City of Hope has purposefully availed itself of the benefits and protections of Delaware law.

13. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and (c) and 1400(b), because Genentech is incorporated, both Defendants do business in the State of Delaware, and HGS intends to market Benlysta® in this District upon approval by the FDA.

## THE CABILLY PATENTS

14. On April 8, 1983, Shmuel Cabilly, Herbert Heyneker, William Holmes, Arthur Riggs and Ronald Wetzel (the "Cabilly Applicants") filed a patent application in the PTO that issued on March 28, 1989, as U.S. Patent No. 4,816,567 (the "Cabilly I Patent").

15. At the time the Cabilly I Patent issued, the Cabilly Applicants had a continuation application (the "Cabilly II Application") pending in the United States Patent and Trademark Office ("PTO"). The PTO issued the Cabilly II Patent on December 18, 2001. On its face, the Cabilly II Patent is assigned to Genentech, and, by certificate of correction, is also assigned to City of Hope.

### *Patent Reexamination*

16. In 2005, two separate requests to re-examine the Cabilly II Patent were submitted to the PTO. The PTO mailed two separate orders granting a request for reexamination, on July

7, 2005 and January 23, 2006. *See* Decision Granting *Ex Parte* Reexamination, Reexamination Control No. 90/007,542 (July 7, 2005); Decision Granting *Ex Parte* Reexamination, Reexamination Control No. 90/007,859 (January 23, 2006). The reexamination proceedings were merged on June 6, 2006.

17. On July 19, 2008, the PTO mailed an Advisory Action, maintaining its final rejection of all claims in the Cabilly II Patent as invalid for reasons including obviousness-type double patenting. *Ex Parte* Reexamination Advisory Action, Reexamination Control Nos. 90/007,859 and 90/007,542 (July 19, 2008).

18. In response to the final rejection, Defendants filed an Appeal Brief on December 9, 2008.

19. After an *Ex Parte* Examiner Interview on February 13, 2009, Genentech amended claims 21, 27 and 32 to overcome the obviousness-type double patenting rejection. *See* Supplemental Amendment Under 37 C.F.R. § 1.550(b), Reexamination Control Nos. 90/007,859 and 90/007,542 (February 13, 2009).

20. On February 23, 2009, the PTO issued a Notice of Intent to Issue a Reexamination Certificate to Genentech, confirming claims 1-20 and 33-36 and allowing amended claims 21, 27 and 32. Notice of Intent to Issue *Ex Parte* Reexamination Certificate, Reexamination Control Nos. 90/007,859 and 90/007,542 (February 23, 2009). On May 19, 2009, the *Ex Parte* Reexamination Certificate Issued for U.S. Patent No. 6,331,415 C1 with amended claims 21, 27 and 32.

***Defendants' Admissions Regarding State of the Art in April 1983***

21. Defendants made a number of admissions in their December 2008 Appeal Brief regarding the state of the art prior to the filing of the Cabilly II Patent application in April 1983. According to Defendants:

a. "[I]n April 1983, the biological mechanisms that controlled expression of foreign DNA and assembly of proteins were not well understood. This lack of understanding was especially true for eukaryotic genes, which were known to be far more complex than prokaryotic genes. As Dr. Harris, one of Owners' experts in this case, explained in his 1983 review paper, 'it is clear that not all the rules governing the expression of cloned genes have been elaborated and those rules that do exist are still largely empirical.'" (Appeal Brief at 20).

b. "In early April of 1983, the field of genetic engineering was still developing . . . . A relatively small number of proteins had been made by recombinant DNA technology. Almost all of those were relatively simple monomeric (i.e., one polypeptide chain) proteins." (Appeal Brief Appendix at B551 [Harris Decl.]).

c. "As of April 1983, insulin was the only 'multimeric' protein that had been made using genetic engineering." (Appeal Brief at 21).

d. "Several experts with actual experience in the field of the invention in April 1983 explained that those references cited by the Examiner that include experimental results show a significant amount of unpredictability in achieving success in simpler experiments than what is required by the '415 patent claims." (Appeal Brief at 28).

e. "[S]uccessful production of immunoglobulins was highly dependent on the sequence of expression and levels at which the two immunoglobulin genes were expressed." (Appeal Brief at 63).

f. "[L]evels of expression of each immunoglobulin gene could affect production of the other immunoglobulin polypeptide." (Appeal Brief at 63).

g. "Such a person would have been familiar with the many complications of producing eukaryotic polypeptides in bacterial host cells known by April 1983." (Appeal Brief at 73).

h. "I believe a person of ordinary skill in the art, in early April of 1983, would have thought that successful expression of two immunoglobulin proteins in one transformed host cell would have been unpredictable and that assembly of the two proteins into an immunoglobulin tetramer would have been even more unpredictable." (Appeal Brief Apendix at B224 [McKnight Decl.]).

i. "Experimental results would have been important to a person of ordinary skill in the art in April 1983 because many of the biological mechanisms that controlled expression of foreign DNA and assembly of proteins were not well understood at that time." (Appeal Brief Appendix at B376 [Second McKnight Decl.]).

j. "Each of these papers shows that successful transformation and expression of even one foreign immunoglobulin gene in a lymphoid host cell could not be reasonably expected in April 1983. I do not believe these references can be read as suggesting that something even more challenging — expressing two different foreign immunoglobulin genes in one transformed cell — would have been something that could be predictably achieved at that time." (Appeal Brief Appendix at B382 [Second McKnight Decl.).

k. ". . . I disagree with the suggestion, that by early April 1983, my PNAS paper had made routine or predictable the task of expressing exogenous immunoglobulin light and heavy chain genes in the same cell. In later experiments, I attempted to use the techniques described in the PNAS paper to introduce and express single Ig genes into other lymphoid cell lines. Most of these experiments failed to produce

stable transfectants. Thus, my experience was that using the same transfection and selection conditions described in the PNAS paper with other cell lines or other Ig genes did not routinely yield stable transformants containing even a single exogenous Ig gene." (Appeal Brief Appendix at B391 [Rice Decl.]).

## HGS'S BENLYSTA® (BELIMUMAB)

22. Benlysta® (belimumab) is a new, human monoclonal antibody that targets the B-lymphocyte stimulator ("BLyS"), a naturally occurring protein, which is involved in the mediation of immunological responses and autoimmune diseases, including Lupus. HGS first discovered BLyS in 1996 and published a scientific article describing its activity in the journal *Science* in July 1999. Following that discovery, HGS initiated a program to develop human monoclonal antibodies that would specifically recognize and inhibit the biological activity of BLyS.

23. After years of research and development, on June 2, 2010, HGS submitted a BLA to the FDA seeking to market Benlysta® with an indication for the treatment of autoantibody-positive patients with Lupus. If approved, Benlysta® would be the first new approved drug for Lupus in more than fifty years.

24. HGS has expended substantial revenues researching and developing Benlysta®. HGS also has expended substantial revenues preparing to launch and commercialize Benlysta®.

25. HGS currently manufactures belimumab in Rockville, Maryland in anticipation of commercial sales in the United States as the Benlysta® product. In addition, copies of the working cell bank used to produce Benlysta® are maintained by HGS in Rockville, Maryland.

26. The FDA Arthritis Advisory Committee met to consider the Benlysta® BLA on November 16, 2010, voting 13 to 2 to recommend that the FDA approve Benlysta®.

27. In the near future, HGS expects a decision from the FDA on the approval of HGS's BLA for Benlysta®. Upon approval, HGS will begin marketing Benlysta® in the United States, including in this District.

**HGS'S DISPUTE WITH DEFENDANTS REGARDING THE CABILLY II PATENT**

28. Through its statements and actions, Genentech has made clear to the biopharmaceutical industry generally and to HGS particularly that it contends that the claims of the Cabilly II Patent preclude others from commercially manufacturing recombinantly produced monoclonal antibodies without Genentech's permission. In 2002, after the Cabilly II Patent issued, Sean Johnston, then Genentech's Vice President of Intellectual Property and now Genentech's Senior Vice President and General Counsel said:

> "The recently issued patent **broadly covers** the co-expression of immunoglobulin heavy and light chain genes in a single host cell . . . We do not believe that the claims are limited by type of antibody (murine, humanized, or human) or by host cell type."

Genentech Awarded Critical Antibody Patent, *Nature Biotechnology*, vol. 20, p. 108 (Feb. 2002) (emphasis added).

29. According to Defendants, the manufacturing methods claimed in the Cabilly II Patent are "the backbone of recombinant antibody production in the biotech industry." *Centocor, Inc. v. Genentech, Inc.*, Case No. 2:08-cv-03573 (C.D. Cal.) (Opening Brief of Claim Construction, March 24, 2009), Dkt. No. 78.

30. Genentech has asserted the Cabilly II Patent in litigation against other manufacturers of recombinant monoclonal antibodies, including MedImmune, Inc., Centocor Ortho Biotech Inc. and GlaxoSmithKline LLC. *See MedImmune Inc. v. Genentech, Inc.*, Case No. 03-cv-02567 (C.D. Cal.); *Centocor, Inc. v. Genentech, Inc.*, Case No. 08-cv-03573 (C.D. Cal.); *Glaxo Group Ltd. v. Genentech, Inc.*, Case No. 2:10-cv-02764 (C.D. Cal.).

31. On information and belief, Genentech contends that the process and certain starting materials used to produce Benlysta® infringe one or more claims of the Cabilly II Patent.

32. Because Defendants have consistently alleged that the use of well-known, conventional recombinant methods to produce monoclonal antibodies in mammalian cell culture is within the scope of claims of the Cabilly II Patent and have asserted the patent against others who are similarly situated to HGS, Defendants' prior statements and conduct necessarily establish an actual and substantial dispute between HGS and Defendants regarding the invalidity, unenforceability and noninfringement of the claims of the Cabilly II Patent. Therefore, HGS has a reasonable apprehension of suit by Genentech and City of Hope regarding the Cabilly II Patent.

33. In addition to the statements and conduct directed at others, Defendants have made statements and engaged in conduct directed at HGS that create a real and immediate dispute between the parties regarding the Cabilly II Patent.

34. Genentech has made public statements about pursuing an aggressive litigation policy to protect its products against competition and to protect against alleged infringement of the Cabilly II Patent claims in its 2009 Form 10-K filing with the Securities and Exchange Commission. Genentech states:

> "Intellectual property protection of our products is crucial to our business. Loss of effective intellectual property protection could result in lost sales to competing products and loss of royalty payments (for example, royalty income associated with the **Cabilly patent**) from licensees. We are often involved in disputes over contracts and intellectual property, and we work to resolve these disputes in confidential negotiations or litigation. We expect legal challenges in this area to continue. We plan to continue to build upon and defend our intellectual property position."

(emphasis added). Genentech also states: "We have in the past been, are currently, **and may in the future be involved in material litigation** and other legal proceedings related to our proprietary rights, **such as the Cabilly patent litigation and reexamination**. . . ." (emphasis added).

35. On January 7, 2011, Defendants averred in a court filing that HGS's process to make Benlysta® infringes the Cabilly II Patent. Specifically, in Defendants' Opening Brief on Claim Construction, a patent infringement action involving GlaxoSmithKline's antibody Arzerra™ and the Cabilly II Patent, Defendants stated:

> "Genentech and City of Hope **intend shortly** to ask the Court for leave to add infringement allegations against a new GSK product, Benlysta® (belimumab), a recombinantly engineered monoclonal antibody for the treatment of lupus. . . . The process used to make Benlysta® is similar to that for Arzerra, except that it uses two vectors instead of one (and thus will implicate claims 18 and 20)."

*Glaxo Group Ltd. v. Genentech, Inc.*, Case No. 2:10-cv-02764 (C.D. Cal.), Dkt. No. 83 at FN4 (emphasis added)

36. Taken together, Genentech's statements that it will enforce the Cabilly II Patent to defend its products against competing products, and Defendants' sworn contention that HGS's Benlysta® infringes at least two claims of the Cabilly II Patent, establish that a real and immediate dispute exists between the parties with adverse legal interests concerning the Cabilly II Patent. HGS therefore has a reasonable apprehension of suit by Genentech and City of Hope regarding the Cabilly II Patent.

## FIRST CAUSE OF ACTION
## NON-INFRINGEMENT

37. HGS incorporates the allegations of paragraphs 1 through 36 as if fully set forth herein.

38. An actual controversy has arisen and now exists between the parties concerning whether HGS's manufacture of Benlysta® (belimumab) infringes any valid and enforceable claim of the Cabilly II Patent, either directly or indirectly, literally, under the doctrine of equivalents, or otherwise.

39. HGS seeks a declaratory judgment that making, using, importing, offering to sell, and selling Benlysta® (belimumab) does not and will not infringe any valid and enforceable claim of the Cabilly II Patent.

**SECOND CAUSE OF ACTION**
**INVALIDITY**

40. HGS incorporates the allegations of paragraphs 1 through 39 as if fully set forth herein.

41. The Cabilly II Patent is invalid because it is anticipated and/or obvious under 35 U.S.C. §§ 102 and 103.

42. The Cabilly II Patent is invalid based on the judicially created doctrine of obviousness-type double patenting and/or under 35 U.S.C. §§ 101 and/or 103.

43. The Cabilly II Patent is invalid under 35 U.S.C. § 112.

44. Claims 21-32 of the Cabilly II Patent are invalid as being broadened in scope during reexamination in violation of 35 U.S.C. § 305.

45. HGS seeks a declaratory judgment that the Cabilly II Patent is invalid under 35 U.S.C. §§ 101, 102, 103, 112 and 305 and/or under the judicially created doctrine of obviousness-type double patenting.

**THIRD CAUSE OF ACTION**
**PROSECUTION LACHES**

46. HGS incorporates the allegations of paragraphs 1 through 45 as if fully set forth herein.

47. An actual controversy has arisen and now exists between the parties concerning the enforceability of the Cabilly II Patent.

48. The Cabilly II Patent is unenforceable under the doctrine of prosecution laches. The Cabilly II Patent issued after an unreasonable and unexplained delay in the interference proceedings between the Cabilly II Application and U.S. Patent No. 4,816,397. Genentech also unreasonably delayed the prosecution of claims 21, 22, 27-30 and 32, which were filed as part of the Cabilly II Application in 1983 but did not issue until 2001.

49. HGS seeks a declaratory judgment that the Cabilly II Patent is unenforceable due to prosecution laches.

## DEMAND FOR JURY TRIAL

50. Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, HGS demands a trial by jury of all issues so triable.

## PRAYER FOR RELIEF

WHEREFORE, HGS requests that judgment be entered in favor of HGS and against Defendants Genentech and City of Hope:

a) Declaring that the manufacture, use, importation, offer to sell, or sale of HGS's Benlysta® (belimumab) product does not infringe any valid and enforceable claim of the Cabilly II Patent;

b) Declaring that the Cabilly II Patent is invalid;

c) Enjoining Genentech and City of Hope from enforcing the Cabilly II Patent;

d) Awarding costs to HGS in accordance with 35 U.S.C. § 284;

e) Declaring HGS's case to be exceptional and awarding HGS its attorneys' fees and expenses under 35 U.S.C. § 285; and

f) Awarding HGS such other relief as the Court may deem just, equitable, and proper.

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