Board of Trustees of the Leland Stanford Junior University v. Roche Molecular Systems, Inc. et al Doc. 93

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

v.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Defendants.

ROCHE MOLECULAR SYSTEMS, ET AL.,

Counterclaimants,

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN AND MARK HOLODNIY

Counterclaim Defendants.

Case No. C 05 04158 MHP

DECLARATION OF MARK HOLODNIY, M.D., IN SUPPORT OF COUNTERCLAIM DEFENDANTS STANFORD UNIVERSITY, DR. MERIGAN AND DR. HOLODNIY'S MOTION FOR SUMMARY JUDGMENT

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I, MARK HOLODNIY, declare:

1. I am a Professor of Medicine at Stanford University. I have an M.D. from Northwestern University, and I completed a fellowship program in infectious diseases at the Stanford University School of Medicine.

2. I am also a named Counterclaim Defendant in this case. I submit this declaration in support of Stanford and Counterdefendants' Motion for Summary Judgment. I have knowledge of the following, and if called as a witness, I could and would testify competently to this declaration's contents.

3. I refer in this declaration to exhibits that are attached to Declaration of Michelle S. Rhyu, to be submitted concurrent with this declaration.

4. I am a named inventor on two U.S. patents: U.S. Patents Nos. 5,968,730 (the "'730 patent") and 6,503,705 (the "705 patent"). Both patents (collectively, "the monitoring patents") are entitled "Polymerase Chain Reaction Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome." These patents generally claim methods for evaluating the effectiveness of anti-HIV therapy to make therapeutic decisions for treating patients with Acquired Immunodeficiency Syndrome (AIDS).

5. I joined Stanford as a post-doctoral fellow in the July of 1988. I spent the first few months in clinical rotations and began focusing on possible research projects in the fall of 1988. In the fall of 1988, I joined the lab of Dr. Thomas Merigan to begin a research project.

6. At the time I started working at Stanford, I signed a Copyright and Patent Agreement. A copy of that agreement is attached to the Rhyu Declaration as Exhibit 23

7. In or around the fall of 1988, Dr. Merigan and I discussed the shortcomings of existing assays for detecting and quantifying the level of HIV DNA in patient samples. We determined that I should direct my research to developing a better quantitative PCR-based assay for HIV than the one that existed at that time. To familiarize myself with the existing methods, I read the available literature relating to PCR assays.

8. My laboratory notebook from the period when I first joined the Merigan lab shows that I had been referring to specific publications and had performed PCR assays on HIV and HLA sequences, using primers that I had ordered from a company, Operon Technologies, in the fall of 1988. A copy of excerpts from lab notebook is attached to the Rhyu Declaration as Exhibits 5 and 7.

9. Many of the PCR-related publications as of 1988 had been published by scientists at Cetus Corp. in Emeryville. At that time Cetus was using a semi-quantitative assay. At some point in 1988 or 1989, Dr. Merigan and I decided that it would be helpful to work with Cetus scientists to develop an HIV assay that was capable of accurately measuring HIV copy number.

10. I understand that Roche claims that I received materials and information from Cetus under a "Materials Transfer Agreement" that was signed by Drs. Merigan and Schwartz. (See Exhibit 29.) I never knew that this agreement existed prior to this case. No one from Cetus or anywhere else ever told me that this Agreement existed, and no one ever indicated to me that they were giving me materials or information under this agreement. I never signed a Materials Transfer Agreement with Cetus.

11. In February of 1989, I started as a visiting scientist at Cetus. Sometime in that timeframe, I signed a Visitor's Confidentiality Agreement that was provided to me. I understood that the agreement concerned my obligations to Cetus' confidential information. I never understood that agreement to cover work that I did when I was not at Cetus and not using confidential information.

12. Starting around February 1989, I spent several days a week at Cetus testing different approaches to quantitation of HIV nucleic acid. I spoke to Alice Wang and Ernie Kawasaki about their work in quantitative PCR and to Shirley Kwok and John Sninsky about their work related to detection of HIV using PCR. I also had some interaction with other Cetus employees, including Michael Konrad, Eric Groves, Sharon DeGroat, Sanne DeWitt, Clayton Casipit, and Sue Kim. When I visited, I worked in the laboratory of Eric Groves and Mike Konrad. None of these people ever told me that our conversations were confidential or that Cetus considered any of our conversations to be about trade secrets.

13. During the time that I visited Cetus, I worked on developing the HIV assay with scientists at Stanford. Although I obtained advice about PCR from Cetus scientists, my understanding is that no one at Cetus was assigned to work on the project with me. Certainly, no one at Cetus directed the work I performed, and Cetus never paid me any wage or salary.

14. During the time I visited Cetus, no one ever told me that any particular information I learned or any reagent I used was confidential. None of the materials given to me were ever labeled confidential. At any given time during this period, I kept a single notebook, which I carried back and forth between Cetus and Stanford. No one requested that I keep a separate notebook for work performed at Cetus, and no one asked me to leave my lab notebook at Cetus, either when I worked at Stanford, or after I stopped being a visiting scientist.

15. I returned to spending full time at Stanford in fall of 1989, after the Loma Prieta earthquake.

16. By fall of 1989, I had developed a working assay that allowed quantitation of HIV RNA copy number from patient serum samples. I continued to refine this assay in the Stanford laboratories with the assistance of Sohini Sengupta, a Stanford lab technician, as well as Drs. Merigan and David Katzenstein.

17. It was and is my belief that the materials and basic protocols shared by Cetus in support of our joint work were not trade secrets or confidential information. The techniques, protocols, and information I learned during my time at Cetus were published prior to my arrival at Cetus, or shortly thereafter, as listed below:

(a) The reverse transcription PCR protocol used by Cetus scientists and disclosed to me at Cetus was published in 1989 in Kawasaki E., *Amplification of RNA*, in: Innis et al., *PCR Protocols: a Guide to Methods and Applications*, Berkeley, CA: Academic Press, 337-47 (1990). The JID article cites this as a prior publication at footnote 8. The Kawasaki article indicates that the first reported use of reverse transcription PCR to amplify RNA had been published in 1987 by Veres et al. in *The Molecular Basis of the Sparse Fur Mouse Mutation*, Science 237:415-17 (1987). Although the citation lists the date of publication as 1990, I

understand that the actual date of publication was December 28, 1989. A copy of that publication is attached to the Rhyu Declaration as Exhibit 640.

(b) The sequences of all four DNA primers used to perform PCR in the JID article, SK 19, SK 38, SK 39, and SK 145, were published in Kellogg D.B., Kwok S., *Detection of Human Immunodeficiency Virus*, in: Innis et al., *PCR Protocols: a Guide to Methods and Applications*, Berkeley, CA: Academic Press, 337-47 (1990). The JID article cites this as a prior publication at footnote 9. Although the citation lists the date of publication as 1990, I understand that the actual date of publication was December 28, 1989. A copy of that publication is attached to the Rhyu Declaration as Exhibit 694.

(c) The sequence of SK 19 primer was also published in 1987 in *Identification of Human Immunodeficiency Virus Sequences by Using In Vitro Enzymatic Amplification and Oligomer Cleavage Detection*, J. Virology, 61(5): 1690-94 (1987). A copy of that publication is attached to the Rhyu Declaration as Exhibit 536.

(d) The sequences of both the SK 38 and SK 39 primers were also published by Shirley Kwok and other Cetus scientists in 1988 in Ou et al., *DNA Amplifcation for Direct Detection of HIV-1 in DNA of Peripheral Blood Mononuclear Cells*, Science, 239:295-297 (1988). A copy of that publication is attached to the Rhyu Declaration as Exhibit 537.

(e) The sequence of the SK 145 primer was also published by Cetus in February 1990 in Kwok et al., *Effects of Primer-Template Mismatches on the Polymerase Chain Reaction: Human Immunodeficiency Virus Type 1 Model Studies*, Nucleic Acids Res., 18(4): 999-1005 (1990). A copy of that agreement is attached to the Rhyu Declaration as Exhibit 695.

(f) Cetus' protocols for biotinylation of SK 38 and horseradish peroxidase (HRP) labeling of SK 19 were published by Cetus in Levenson C., Chang, C., *Nonisotopically Labeled Probes and Primers*, in: Innis et al., *PCR Protocols: a Guide to Methods and Applications*, Berkeley, CA: Academic Press, 1990:337-47 (1990). The JID article cites this as a

prior publication at footnote 10. Although the citation lists the date of publication as 1990, I understand that the actual date of publication was December 28, 1989. This publication, which is a review article, establishes that the basic methods for labeling PCR primers with biotin and HRP had been described in scientific literature as early as 1985 and 1988, respectively. A copy of that publication is attached to the Rhyu Declaration as Exhibit 696.

(g) Isotopically labeled SK 19 was disclosed in 1987 in Kwok et al., *Identification of human Immunodeficiency Virus Sequences by Using In Vitro Enzymatic Amplification and Oligomer Cleavage Detection*, J. Virology, 61(5):1690-94 (1987). A copy of that publication is attached to the Rhyu Declaration as Exhibit 536.

(h) The method of quantitative RT-PCR developed by Alice Wang was disclosed by Cetus in 1989 in Wang et al., *Quantitation of mRNA by the Polymerase Chain Reaction*, Proc. Natl. Acad. Sci., 86:9717-21 (1989). This publication disclosed the construction and use of an internal standard similar to the CC1 and CC2 RNA standards. A copy of that publication is attached to the Rhyu Declaration as Exhibit 12.

(i) The method of quantitative RT-PCR developed by Alice Wang was also disclosed by Cetus in Wang A., Mark D, *Quantitative PCR*, in: Innis et al., *PCR Protocols: a Guide to Methods and Applications,* Berkeley, CA: Academic Press, 1990:70-75 (1990). Although the citation lists the date of publication as 1990, I understand that the actual date of publication was December 28, 1989. This publication also disclosed the construction and use of an internal standard similar to the CC1 and CC2 RNA standards. A copy of that publication is attached to the Rhyu Declaration as Exhibit 697.

18. With assistance from both Stanford and Cetus scientists, I ultimately developed an improved PCR assay for quantitating HIV RNA. One important difference between this assay and preexisting assays developed by Cetus is that this assay focused on HIV RNA sequences in patient serum, whereas prior Cetus assays had looked at detection of HIV in peripheral blood mononuclear cells. The decision to redirect the focus of my research to RNA

quantitation in serum rather than DNA quantitation in cells was made without any input from Cetus scientists.

19. In or around December 1989, I prepared an abstract describing this research on a quantitative PCR assay for the UCLA Keystone Symposium on Molecular and Cellular Biology. This abstract was published, after obtaining Cetus' consent, under the title *Quantitation of HIV-1 RNA in Serum and Correlation with Disease Status Using Polymerase Chain Reaction*, in the Journal of Cellular Biochemistry, 14D (1990). The article lists Cetus scientists Alice Wang, Clayton Casipit, Mike Konrad, and Eric Groves as co-authors. I presented the abstract at the Keystone Symposium in March or April of 1990. A copy of that abstract is attached to the Rhyu Declaration as Exhibit 698.

20. Around the same time, I submitted an invention disclosure form to Cetus describing the assay for quantitating HIV RNA in serum that I had worked on at Cetus. A copy of this invention disclosure form is attached to the Rhyu Declaration as Exhibit 34. Other than the request to fill out this disclosure form, Cetus never communicated to me any interest in patenting the described invention. I concluded that Cetus was not interested in pursuing further development of the RNA quantitative assay.

21. In early 1990, with Cetus' consent, Dr. Merigan and I prepared a second abstract describing the assay. We presented this abstract at the Sixth International AIDS Conference in San Francisco in 1990, listing Cetus scientists Alice Wang, Clayton Casipit, Mike Konrad, and Eric Groves, as well as Stanford researchers Sohini Sengupta, David Katzenstein, and David Schwartz, as co-authors. I presented the abstract at the AIDS conference in San Francisco in June 1990. A copy of that abstract is attached to the Rhyu Declaration as Exhibit 699.

22. By May of 1990, I had prepared a manuscript detailing the quantitative assay for HIV RNA in patient serum. I forwarded that manuscript to Eric Groves at Cetus for his review prior to submitting it. The manuscript was published with Cetus's consent in the *Journal of Infectious Diseases*, 163(4):862-66, in April 1991 under the title *Detection and Quantification of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction*. ("JID article.") The article lists Cetus scientists Alice Wang, Clayton Casipit, Mike

Konrad and Eric Groves as co-authors. This publication is discussed in the disclosure of the Merigan patents. A copy of that manuscript is attached to the Rhyu Declaration as Exhibit 1. Based on Cetus' consent to publish the JID article and the two earlier abstracts, I concluded that the work done on the assay was within the public domain.

23. Around the same time period, I discussed with Dr. Merigan and other scientists at both Stanford and Cetus a phenomenon involving the inhibition of PCR reactions by heparin. In collaboration with Cetus scientists, including Sue Kim, a technician at Cetus, we verified this inhibitory effect. Cetus never asked me to keep the heparin work confidential. In July 1990, with Cetus' consent, we submitted a manuscript describing this research to the Journal of Clinical Microbiology. This work was published under the title *Inhibition of Human Immunodeficiency Virus Gene Amplification by Heparin*, Journal of Clinical Microbiology, 29(4):676-79 (1991) ("JCM article"). A copy of that manuscript is attached to the Rhyu Declaration as Exhibit 13.

24. I stopped visiting Cetus on a regular basis in October or November of 1989. I subsequently made only a handful of visits to Cetus, primarily to complete the work on the PCR assay and heparin inhibition. The *JID* article and the *JCM* article represent the end of my joint work with Cetus.

25. In July 1990, following submission of the JID article, I began experiments to ascertain whether HIV RNA levels in patient serum or plasma samples would correlate with the effect of HIV treatment and would inform decisions regarding patient treatment. All of my research from July 1990 going forward was performed at Stanford .

26. While the methods for evaluating the effect of anti-HIV therapy described in the monitoring patents involve using a quantitative PCR assay, the PCR method itself is not the invention claimed in the patents.

27. Despite our work on the HIV RNA quantitation assay, it was quite unclear in mid 1990 whether the quantitation technique would work reliably to detect responses to antiviral therapy. For example, there was widespread uncertainty at the time about whether the assay would be sufficiently sensitive and reproducible to measure HIV RNA changes over time in a

clinical setting. It was unclear whether the variability of virus levels and changes in virus levels for different individuals would be detectable using this assay. There was much uncertainty in the field about whether nucleic acid levels in plasma could be used to predict the effectiveness of the therapy. There was also an overriding concern about whether the available treatments would be strong enough to produce changes that could be measured.

28. In addition to the uncertainties described above, there were a number of factors that had not yet been worked out. Appropriate patient samples needed to be identified and obtained. The quantitative assay needed more refinement to improve sensitivity and reproducibility. Further improvements were made to the process of HIV RNA extraction from patient samples. We performed experiments to establish that samples could be stored for prolonged periods of time without degradation of HIV RNA. The assay then had to be performed in parallel with tests that could independently verify the effect of treatment. Statistical analyses had to be performed on the results obtained from the patient samples to determine whether there was, in fact, a correlation between the effectiveness of treatment and HIV levels.

29. Drs. Merigan, Katzenstein, and I designed and carried out these experiments, with some assistance from Dr. Dennis Israelski, who provided patient samples. Cetus was not involved in any stage of the effort to design or carry out these clinical experiments. We designed the original experiments to test samples from patients who had been treated with a drug called dideoxyinosine, both by itself and in combination with AZT. Drs. Merigan, Katzenstein, and I worked on this through the summer and winter of 1990. By early 1991, we had demonstrated a correlation between HIV levels and the effectiveness of treatment.

30. In May 1991, Drs. Merigan, Katzenstein, Israelski, and I submitted a manuscript to the Journal of the Clinical Investigation (JCI) describing our findings. The article, *Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid after Dideoxynucleoside Therapy as Determined by the Polymerase Chain Reaction*, Journal of Clinical Investigation, 88(5):1755-59 ("JCI article"), was published in November 1991. The article reports that a correlation could be made between the effect of anti-HIV therapy and HIV RNA level, enabling the use of the

correlation to make therapeutic decisions for treating AIDS patients. The work described in the JCI article is the central work on which the monitoring patents are based.

31. Based on the fact that the JCI manuscript was received by the journal on May 14, 1991, I am confident that the substantive work reported in the article was completed before April 19, 1991. It would have taken me at least a month and likely two months from the time I completed the experiments to write the manuscript, distribute the manuscript to my coauthors for their comments, to incorporate their comments, and to prepare the final manuscript and figures for submission.

32. Since 1989, I have had interactions with John Sninsky at conferences and scientific meetings. We have discussed the method of monitoring the effectiveness of HIV therapy using PCR on numerous occasions. He has never indicated to me that he believed that Cetus deserved any credit for this work. He has never indicated to me that he believed that Cetus or Roche had any ownership interest in this work.

33. Prior to this suit, no one else at Cetus or Roche communicated to me that they believed the work described in the *JCI* article should be attributed to Cetus or Cetus' scientists.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed in Palo Alto, California on October 27, 2006.

Mark Holodniy, M.D.

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