IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Gallo et al,

v.

Montagnier et al,

Interference No. 101,574
Examiner-in-Chief: N.G. Torchin

BOX INTERFERENCE
Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

DECLARATION OF
Robert C. Gallo

I, Robert C. Gallo, declare the following:

(1) I am the Robert C. Gallo who is listed with Mikulas Popovic and Mangalasseril G. Sarngadharan as joint inventor of the invention described and claimed in U.S. patent 4,520,113 which is involved in Interference No. 101,574;

(2) My education includes a B.A. degree in Biology summa cum lauda from Providence College, Providence, Rhode Island in 1954 and an M.D. degree with honors from Jefferson Medical College, Philadelphia, Pennsylvania, in 1963.

I then served a clinical clerkship at the Yale University School of Medicine, New Haven, Conneticut and from 1963 to 1965 I was an intern and resident in medicine at the University of Chicago. From 1965 to 1968, I served as a clinical associate in the Medicine Branch of the National Cancer Institute (NCI), Bethesda, Maryland and from 1968 to 1969 I was a senior investigator in the Human Tumor Cell Biology Branch of NCI. Thereafter, from 1969 to 1972, I was the Head of the Section on

Cellular Control Mechanisms, Human Tumor Cell Biology Branch, NCI, and from 1972 to date I have been the Chief of the Laboratory of Tumor Cell Biology, Development Therapeutics Program at NCI.

(3) I have received honorary doctorate degrees from Providence College; Thomas Jefferson University; University of Rochester; University of Turin (Italy); Temple University Hospital; University of Medicine & Dentistry of New Jersey; and Tel Aviv University of Israel. I am an honorary and/or adjunct professor at Johns Hopkins University, Baltimore, Maryland (Biology Department), at George Washington University in Washington, D.C. (Genetics) and at Cornell University School of Veterinary Medicine, Ithaca, New York (Virology). I have also served on a number of editorial broards, received numerous scientific awards and published over 680 papers, as shown in my Curriculum Vitae, attached as GX-1;

(4) The invention of U.S. Patent No. 4,520,113 is concerned with the detection of antibodies to the AIDS virus in human sera by immunoassay means based on the use of the virus known as HTLV-III. An essential feature of the invention was the discovery that HTLV-III is the cause of AIDS. A person who has AIDS develops antibodies in his blood which are specific to AIDS virus. By finding that the virus we call HTLV-III is the cause of AIDS, it became possible, once we had also found how to produce the virus in relatively large amounts of consistent

composition to develop the detection method described in U.S. Patent No. 4,520,113. Such method has made it possible to screen blood, for example, the blood in blood banks, to be sure the blood is free of AIDS virus. Until the discovery of the cause of AIDS and the development of this test, hemophiliacs and others requiring blood transfusions ran a very real risk of getting AIDS when receiving blood. The test has essentially eliminated this risk;

(5) As indicated in paragraph 4, it was essential in the development of the test to find a way of producing HTLV-III in relatively large amounts and in reproducible composition. This was essential initially for the positive identification of the virus as the cause of AIDS and then as the means for providing a standardized and reliable antigen composition for the test itself. The AIDS virus is cytopathic in the sense that it kills the T-cells which would normally be used to co-cultivate with the virus to produce more virus. Because of this, much of our effort at NCI, after we became aware that a new retrovirus might be involved, as discussed later herein, was directed towards finding a way of producing the retrovirus so that we could have enough to isolate it, examine its protein components, develop specific reagents to demonstrate that any two isolates were one and the same virus type, and test against AIDS sera. After difficult and extensive research throughout 1983, my coworker, Dr. Popovic, discovered some cell lines which were

"permanent", i.e. not killed by the virus, and could be effectively used to reproduce the virus. Such a permanent cell line is disclosed in U.S. 4,520,113. See, for example, column 2, lines 39-61 of the patent.

(6) A brief summary of the work done by my colleagues and I leading to U.S. Patent 4,520,113 is set forth below. However, as a preliminary point, it may be useful to note that HTLV-III is a so-called retrovirus. Such a virus is one which utilizes an enzyme known as reverse transcriptase to change the RNA of the virus into DNA. The thus transcribed DNA can then become integrated into a host cell where it replicates itself.

(a) Reverse transcriptase was discovered in 1970 by Dr. Temin and his colleagues at the University of Wisconsin in Madison and Dr. Baltimore at MIT. This opened up the way for studies into the molecular biology of retroviruses.

(b) In 1970-1975, my colleagues and I at NCI, and the late Sol Spiegelman of Columbia University used reverse transcriptase to establish an assay for determining the presence of a retrovirus in cells, especially for finding a retrovirus present in very small amounts, i.e. very sensitive and specific tests for this enzyme were developed. We used this assay extensively and were the first to apply it to human cells in the search for retroviruses. The assay was widely published and it has turned out to be one of the critical and essential methods for the discovery of all human retroviruses.

(c) In 1976, my colleagues and I at NCI published on our discovery in 1975 of a T-cell growth factor (now called interleukin-2 or Il-2). This factor permitted the routine long-term growth of normal and malignant T-cells in culture for the first time. This discovery too proved to be critical for the first and all subsequent identifications of human retroviruses.

(d) The first human retrovirus (HTLV-I) was discovered by my colleagues and I at NCI in 1978 in patients suffering a certain type of leukemia characterized by the proliferative growth of T-cells. The discovery resulted from the use of the reverse transcriptase assay and T-cell growth factor (interleukin-2) referred to above. Along with Japanese colleagues, we subsequently established that this retrovirus was the cause of the leukemia and we called the virus, the human T-cell leukemia virus, or HTLV for short. We published this 1978 work on HTLV-1 in 1980. I believe this was the first human retrovirus to be isolated and identified. We subsequently obtained many more isolates in 1980-81, and this work was confirmed by many groups.

My colleagues at NCI and I, working together with Dr. David Golde of UCLA, also later isolated a different human retrovirus from cells of patients with hairy cell leukemia. This was called HTLV-II, and the first retrovirus we had earlier identified then became known as HTLV-I.

(e) I proposed the possibility that a retrovirus was the cause of AIDS at several meetings in early to mid-1982. This suggestion was even published in Medical World News, August, 1982, copy attached as GX-2. By December, 1982, our group at NCI detected a new retrovirus in AIDS sera which appeared to be different from HTLV-I and HTLV-II. This retrovirus was ultimately called HTLV-III after we were able to mass produce it, characterize it and determine that it was the cause of AIDS. At the time, however, it was not possible to do the necessary biology to produce or characterize the new retrovirus because we could not get the virus to grow using conventional co-cultivation techniques. We did know, however, that this new virus was a retrovirus because we had noted reverse transcriptase (RT) activity and we also knew that this retrovirus was different from HTLV-I and HTLV-II because of its cytopathic nature and its failure to react with HTLV-I and HTLV-II reagents.

(f) Subsequently, in February 1983, a further detection of the virus which would later be called HTLV-III was made which this time included electron microscopy as well as RT, and negative reaction with HTLV-I and II reagents. Approximately 25-30 further instances of the detection of this new retrovirus occurred in the period up to September, 1983. Most, if not all of these isolates were retained for examination as further reagents which might be used to characterize and identify the virus became available through our ongoing work.

(g) At this stage, the indications were that the virus in question might be related to HTLV-I although different therefrom, and we continued our work in that direction using the probes and techniques we had developed in our work with HTLV-I and HTLV-II. This was, of course, all that we had available to use since, in view of the inability to grow the virus, no one had any specific reagents to type the virus. At the same time, however, i.e. in early 1983, my colleague Dr. Popovic took on the task of trying to find a way of growing the new retrovirus. This was a difficult project because the retrovirus was cytopathic and appeared to kill any cells which were selected for use. Ultimately, however, in the fall of 1983, Dr. Popovic discovered that a few cell lines but in particular a cloned cell line, designated H9, was resistant to the retrovirus and could be effectively used to produce the virus in relatively large amounts of a consistent composition. Dr. Popovic accomplished this by November, 1983 and we (particularly Dr. Sarngadharan and some of my post-doctoral fellows) then proceeded to isolate the protein components of the virus, to use these to test for antibodies in AIDS sera, and develop the specific reagents (monoclonal and hyperimmune antibodies) for the virus.

(h) Such tests or sera from patients with AIDS, patients without AIDS, and patients infected with other types of virus were carried out in December, 1983 - January, 1984, and we were satisfied from the results that we not only had conclusively

determined that this new retrovirus, called HTLV-III, was the cause of AIDS but also that we had an effective test for detecting antibodies to this retrovirus in sera. For example, we gave the results of blind studies, which we performed on panels of sera samples, received from clinical collaborators and from the Center for Disease Control (CDC), to these collaborators and to Dr. Curran of CDC. The results were given to Dr. Curran at a meeting in March, 1984, after an earlier meeting scheduled for February, 1984 with Dr. Curran was cancelled because of the weather. After checking the results, Dr. Curran indicated to me that, in his view, we had determined the cause of AIDS. This was subsequently announced to the public on April 23, 1984, the date the Gallo application for patent was filed.

(7) In the meantime, in the period January to March, 1983, I provided Montagnier and the Pasteur group in France with samples of our HTLV-I and HTLV-II reagents for use in work they indicated they were beginning to do with retroviruses. Earlier I had supplied them with samples of Il-2 for growing T-cells. As I understood it, the virus reagents I sent to them were to be used to check against a retrovirus Pasteur had detected. On May 20, 1983, Pasteur (Barre-Sinoussi, Montagnier and others) published a paper in Science (Montagnier Exhibit 15-hereinafter, referred to as the "Barre-Sinoussi" paper) which reported on a retrovirus which had been detected in the cells of a lymph node of one patient with multiple lymphadenopathies. The data provided

electron micrographs, inadequate to warrant publication. In fact several leading virus electron microscopists in the U.S. and France openly took the position that the virus shown was not a retrovirus but an irrelevant arena virus.

(9) In the same May 20, 1983 issue of Science in which the Barre-Sinoussi paper appeared, my colleagues and I at NCI published a paper (GX-5) which described an HTLV-I-like retrovirus in two of 33 AIDS cases. At that time, I thought that the best idea of the causative agent of AIDS was most likely to be a new variant of HTLV-I. However, it is important to understand that at that time we knew we had detected a very different retrovirus (later called HTLV-III), but we did not have adequate reagents to type the new virus or do what we considered was necessary to specifically identify it and to publish on it. As is now well known, AIDS patients are always infected with HTLV-III but frequently are also infected with HTLV-I or HTLV-II. Thus, a mixture of retroviruses can be present. Our thinking at the time was that the AIDS virus was likely to be a close relative of HTLV-1. Indeed, the statement in the Barre-Sinoussi paper that the virus they observed was related to HTLV-I supported this thinking. I also noted that Montagnier and others in a paper published July 20, 1984 in Science, copy attached as GX-6, mention that studies had shown LAV to be more closely related to HTLV-II than to HTLV-I. However, it was clearly evident to me that, as of May 20, 1983, we had detected a

retrovirus different from both HTLV-I and HTLV-II.

(10) I received a sample of LAV from Montagnier in July, 1983. However, on examination by RT assay and nucleic acid (RNA) analysis, we could find no detectable virus in the sample, and Montagnier was so informed. Subsequently some minute viral activity was noted in the sample but this was so small that nothing could be done with the sample. I have no way of knowing whether or not this sample of LAV was the same as the LAV which Montagnier indicates in his patent application was deposited at the Collection of National des Cultures de Micro-organisms (C.N.C.M.). I do know, however, that the sample I received did not show any meaningful viral activity. Probably the bulk of virus in the sample was destroyed in transit from France.

(11) I received another sample of LAV from Pasteur in September, 1983. That sample was found to be viral by checking for reverse transcriptase activity. An attempt was made to co-cultivate the LAV with human cord blood T-cells in the same way as we had done with HTLV-1 and HTLV-II. However, only transient transmission was obtained, and the cells soon died. At that time, and since early 1983, my colleague Dr. Popovič had been trying to develop a permanent cell line by which HTLV-III could be grown in significant amount for further tests and for the development of specific reagents, e.g. purified protein components of the virus. By November, 1983, Dr. Popovic had found that a cell line identified as H9 could be so used to

produce HTLV-III. He tried the H9 cell line with LAV but was not able to produce virus with that cell line. Dr. Popovic did succeed in temporarily transmitting LAV to a cell line called HUT 78 and one other T-cell line. However, both transmissions were only temporary in nature.

(12) With the H9 cell line functioning to produce HTLV-III, we were then able to examine more fully the many isolates which we had earlier placed in our laboratory freezer. These studies made it possible for us to prove that HTLV-III was the cause of AIDS in the period from around December 1983 to February 1984. Our results were published in a series of 4 papers in Science in May, 1984 and one in Lancet in June, 1984, following the filing of our patent application and a public announcement on April 23, 1984. Copies of these papers are attached as GX-7.

(13) In May, 1984, my colleague at NCI, Dr. M.G. Sarngadharan, one of the joint inventors in the Gallo patent, visited the Pasteur Institute in France. Dr. Sarngadharan took with him to give Pasteur various reagents including our H9 cell line producing HTLV-III. Dr. Sarngadharan met with Dr. Montagnier and among other things, discussed the differences between LAV and HTLV-III. I have seen a table signed by Dr. Montagnier which argues for significant differences between HTLV-III and LAV. A copy of that table is attached as GX-8.

(14) I should point out that our group at NCI did not do its own electron microscopy in the period referred to in the foregoing. Up to about September, 1983, samples to be examined by electron microscopy were sent to Electronucleonics, Inc. for examination. However, after September, 1983, we began to use facilities in Frederick, Maryland, specifically operations under contract with Program Resources Incorporated. This included the LAV sample received from Pasteur in September, 1983 which was sent to Frederick labeled as LAV. I understand that a number of electron micrographs were made of the LAV at Frederick. Somehow, one of these was inadvertently used by the Frederick facility in making a composite to show steps of maturation of HTLV-III. Other electron micrography of the AIDS virus, published by our group at this time, included bona fide isolates of HTLV-III from our laboratory.

(15) At the time the Gallo patent was filed, my colleagues and I did not consider LAV and HTLV-III to be the same, or even substantially the same, virus. Quite clearly the data available to us indicated that the two viruses functioned differently and reacted differently. One such difference was shown by the fact that we could grow the HTLV-III using the H9 cell line, and we could not do this with LAV. The second was that the Pasteur group reported a major cross reaction with HTLV-I. We could not find any major cross reaction of HTLV-III with HTLV-I. A third difference was the report in July 1984 by the

Pasteur group which claimed extensive nucleic acid homology of nucleic acid sequences of LAV with HTLV-II and HTLV-I. We found only some marginal homology of HTLV-III with HTLV-I and II. A fourth difference was that the sera of 20% or less of AIDS patients reacted positively with LAV. We found 88% to 100% of these sera positive to HTLV-III. A fifth difference was the claim of Montagnier that LAV did not have a glycoprotein of molecular weight 41,000 Daltons (p41). Nothing of this size was seen by him with LAV. We found p41 in all HTLV-III isolates, and we had evidence that it was a key component of the envelope of the virus and a critical component of our blood test. Finally, I was satisfied that HTLV-III had been proven to be the cause of AIDS, but I saw no evidence of this for LAV up through the allowance of the Gallo patent.

(16) With respect to the Barre-Sinoussi paper in 1983, this did not indicate anything to me as to the cause of AIDS or the possibility of a blood test for it using HTLV-III or, for that matter, any other retrovirus. It was certainly not proven to me that the isolate referred to by Barre-Sinoussi had any significant relationship to the retrovirus I had previously noted.

(17) I do not know, and cannot determine, if the LAV I received from Pasteur in September, 1983 was the same as, or different from, the isolate referred to in the Barre-Sinoussi paper, the isolate referred to by Dr. Montagnier in his

presentation at Cold Spring Harbor in September, 1983, the isolate referred to in the Montagnier patent applications or the isolate deposited at the C.N.C.M. However, in the absence of a permanent cell line to produce a standardized composition, I would expect there to be significant compositional variations resulting, for example, from repeated virus infections (change may occur in the virus genome), the use of different human cord blood cells (therefore, different cell membranes determinants from differences in genetics of each baby), all of which give a variation in cell debris and hence in background noise.

(18) Our group at NCI did not provide CDC with any HTLV-III prior to the disclosure of our test results to Dr. Curran in March, 1984.

(19) As far as I know, the LAS patient from whom the Pasteur group obtained the isolate referred to in the Barre-Sinoussi paper did not have AIDs and apparently never got AIDS.

(20) The normal time lag for publishing work done by our group at NCI is about 1-2 years from the time of detecting something new. for example, our publications on HTLV-I, HTLV-II, II-2 and a new virus known as HBLV occured 2 years, 1 year, 1 year and 1½ years, respectively, after the initial discoveries. This is consistent with the timing of our publications on HTLV-III as the cause of AIDS and our blood test using this virus.

(21) Attached as GX-9 is a copy of my letter dated July 3, 1984 to Dr. Montagnier at Pasteur. This letter lists reagents

and materials which we had supplied to Pasteur. The letter also shows that comparisons between HTLV-III and LAV to determine whether or not these were the same or different were still under consideration as of the date. These discussions about making such comparisons continued on even later through 1984.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code [redacted] such willful false statements may [redacted]rdize the validity of the Gallo patent.

Further declarant sayeth not.

Date: 11/8/86 Robert C. Gallo

Robert C. Gallo