

Department of Health and Human Services

Departmental Appeals Board

RESEARCH INTEGRITY ADJUDICATIONS PANEL

SUBJECT: Mikulas Popovic, M.D., DATE: November 3, 1993
Ph.D.
Docket No. A-93-100
Decision No. 1446

DECISION

Mikulas Popovic, M.D., Ph.D. requested a hearing on the finding of the Public Health Service's Office of Research Integrity (ORI) that he had engaged in scientific misconduct when reporting scientific methods and data in a 1984 paper. ORI deemed the alleged misconduct "relatively minor" and proposed responsive measures which may be similarly described: rather than debarment from federal research funding, ORI proposed to require only a three-year period of "close supervision" of Dr. Popovic's laboratory work.

In spite of the narrow focus of this proceeding, this case has compelled us to parse a record reflecting years of investigations, thousands of pages of documents and lawyers' briefs, a hearing which lasted 12 days, and the time, attention, and disagreement of dozens of scientists, investigators, and lawyers -- all focused essentially on the meaning which we should give a handful of words and notations contained in one heavily-edited paper written by a scientist with limited English skills during a volatile period of scientific discovery a decade ago. The paper in question, it is undisputed, made a major and lasting contribution to establishing that a retrovirus was the etiological agent of AIDS -- even assuming the most ambitious reading of error into the parts in question here.

One might anticipate that from all this evidence, after all the sound and fury, there would be at least a residue of palpable wrongdoing. That is not the case. On reviewing this lengthy record and all the evidence and argument related to each of ORI's allegations, and notwithstanding the vigorous efforts of ORI counsel, we find that ORI was simply unable to prove by a preponderance of the evidence that Dr. Popovic is guilty of scientific misconduct -- even under standards first promulgated years after the paper was published.

As we describe below at length -- in fact, in detail which represents the first time after all these years that there has been a comprehensive, independent review of all the evidence, tested in the fire of full confrontation by Dr. Popovic -- ORI's findings, individually and collectively, contained fundamental flaws: for example, ambiguous language is read one way among other credible possibilities, and such choices in turn become untested assumptions underlying other evidence and expert testimony.

How could it happen that such a massive effort produced no substantial evidence of its premise? Part of the answer may be that early on, investigators' attention was on controversies related to misappropriation of the French LAV virus, the conduct of other scientists, and a patent dispute -- matters which, it is important to note, are not in dispute here but which were regarded as extremely serious. This dispute is largely vestigial. Undoubtedly, many factors may have played a part: the long and disputatious course of this case, difficulties involved in reconstructing events that occurred years earlier, repetitive reviews, layering and bootstrapping of evidence, complexity of the issues, and human nature. Whatever the cause, we can assure both ORI and Dr. Popovic of this: we have carefully considered each and every argument and item of evidence in this record -- individually and collectively -- and we have concluded that the record does not support a finding of scientific misconduct.

Immediately following is a summary of our decision. After that, we give an overview of the legal and factual framework before proceeding to our detailed analysis.

SUMMARY

The ORI findings of scientific misconduct involve a paper published in 1984 in Science magazine, "Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS." Dr. Popovic was the first listed author and principal researcher for the experimental work reported. This paper and three companion papers published in the same issue of Science are regarded as a "tour de force" of science. The paper in question is regarded as a seminal work, possibly the most important paper in virology in the 20th century. Together the four papers established that a retrovirus was the cause of acquired

immune deficiency syndrome (AIDS). The Popovic Science paper reported on a cell system which could continuously produce this retrovirus. Dr. Popovic's success in establishing this cell system permitted more detailed study of the virus as well as development of the blood test needed to ensure the safety of donated blood supplies.

The Popovic Science paper was subject to intense scrutiny as part of an investigation lasting three years. This investigation focused primarily on allegations made in a 1989 newspaper article that the laboratory where Dr. Popovic was employed, the Laboratory of Tumor Cell Biology at the National Institutes of Health (NIH), had misappropriated an isolate of the AIDS virus from the Pasteur Institute in France. In a final report issued December 29, 1992, ORI found that one sentence and seven data points in the Popovic Science paper had been falsified.¹ However, ORI stated:

The confirmed scientific misconduct on the part of Dr. Popovic is relatively minor, does not invalidate the findings of his breakthrough research, and should not preclude his employment as a scientist.

ORI Final Report at 61. Dr. Popovic appealed the ORI findings.

Under the guidelines for these cases, we held an evidentiary hearing. ORI had the burden of proving by a preponderance of the evidence both that Dr. Popovic committed scientific misconduct, and that ORI's proposed administrative action, close supervision, was appropriate.

Based on the record before us, we conclude that ORI did not prove by a preponderance of the evidence that Dr. Popovic committed scientific misconduct. Specifically, ORI did not prove that the Science paper contains untrue statements or data, much less that it contains intentional falsifications.

¹ In this decision, we use the acronym ORI to refer not only to the current Office of Research Integrity, but also to other investigative offices which worked on this matter and which the Office of Research Integrity replaced, including the Office of Scientific Integrity.

A. GENERAL FLAWS IN ORI'S CASE

We found the following general flaws in the evidence ORI presented:

o Each of the findings of scientific misconduct was based on reading in a particular way language which, in context, was merely ambiguous. ORI's reading of that language was developed when the focus of the investigation was on entirely different issues. Overall, the testimony at the hearing did not support ORI's reading. Testimony by the expert scientific advisors on whom ORI relied in reaching its ultimate conclusions merely reflected ORI's reading rather than a critical examination of the actual language in context.

o The opinions given at the hearing by ORI's scientific advisors were based on misunderstandings about what was involved in the research at issue and what Dr. Popovic and others had said. While these advisors were experts with impressive credentials, they were not asked by ORI to conduct a first-hand investigation. Their information was largely derived from the ORI investigators' understandings, which in some instances ignored or misrepresented evidence in the record. Moreover, none of these advisors had direct experience isolating a novel retrovirus. Since their opinions were based on a number of erroneous assumptions, they were largely irrelevant. Testimony by the one retrovirologist who testified for ORI who could be considered a disinterested expert supported Dr. Popovic's case more than ORI's.

o These advisors drew unreasonable inferences from the non-scientific evidence in the case. For example, one scientific advisor inferred that since the English in other papers by Dr. Popovic was "pretty good," he was not credible in claiming that he could not understand the nuances of the language at issue. This inference is unreasonable. Unrebutted evidence shows that some papers by Dr. Popovic had been translated by others from his native language, that some papers were heavily edited, and that Dr. Popovic's English skills were in fact limited at the time he drafted the Science papers (which also was subjected to substantial editing).

o ORI and its experts also did not have a clear idea of the proper legal and scientific standards to apply to Dr. Popovic's conduct. They faulted him simply for doing things differently from how they would have done things. In evaluating Dr. Popovic's conduct against their own, they also applied their experience in other disciplines in a way that failed to take into account the nature of

the experiments reported in the Science paper at issue and the status of AIDS research at the time.

o ORI gave an importance to the matters at issue here which is not justified when the paper is examined as a whole. None of the matters here has any significance to the validity of the major conclusions of the paper. ORI's advisors were clearly frustrated by the difficulties in addressing the issues raised by the 1989 newspaper article. This may have led them to consider out of context the method and data at issue here.

Next we summarize our determinations in relation to each of ORI's particular findings.

B. ORI'S PARTICULAR FINDINGS

ORI'S FIRST FINDING CONCERNS THE FOLLOWING SENTENCE, IN A PARAGRAPH DESCRIBING INFECTION OF A PARENTAL T-CELL LINE: "THE CONCENTRATED FLUIDS WERE FIRST SHOWN TO CONTAIN PARTICLE-ASSOCIATED RT [REVERSE TRANSCRIPTASE]." ORI found that this sentence was false because ORI found that cell cultures from individual patients with AIDS or pre-AIDS were not shown to be RT positive before the cell cultures were used to infect the T-cell line. This finding was based on ORI's reading the term "concentrated fluids" to mean individual patient samples and the "first" to be intended to establish a priority in the timing of the RT tests compared to the infection.

1. We conclude that ORI's first finding is not supported by a preponderance of the evidence, for the following reasons:

o The evidence as a whole shows that the "first shown" sentence does not necessarily have the meaning ORI ascribed to it. ORI's reading ignored Dr. Popovic's and others' consistent explanations of what was meant by the term "concentrated fluids" in that sentence: the fluids that were first pooled and then concentrated for each of the three infections of the same cell line recorded in Dr. Popovic's notebook. At the hearing, ORI presented no evidence to support its assumption that the fluids were concentrated before pooling -- indeed, some evidence ORI presented undercuts that assumption because it indicates that it would have made more sense to pool the fluids before concentrating them. ORI's reading of the purpose of the word "first" in that sentence is also not the only reasonable reading, when considered in context. The point of the paragraph was to establish that the virus

had been transmitted from patient fluids to the parental T-cell line.

o While ORI established generally that there would have been some reason to test for RT activity before pooling patient cultures, ORI did not establish that Dr. Popovic would have viewed not doing so as illogical. Dr. Popovic's explanation of why he pooled fluids from the patient cultures is reasonable, not directly rebutted, and supported by other evidence which shows it is a technique that he would likely have used in a practical sense to isolate a suspected retrovirus.

o ORI did not establish that Dr. Popovic drafted the "first shown" sentence, that his attention was drawn to it during the editing process, or that, even if he noticed it, he would have recognized that it might have been misinterpreted by others. The evidence shows that many others were involved in editing the paper, that the sentence may have resulted from a purely editorial change, and that Dr. Popovic did not have the skills in English to recognize subtle distinctions in meaning.

o ORI did not show that the paragraph in which the sentence appears is the methodological section of the paper, or that Dr. Popovic would have had a motive to falsify his methods. The paragraph in question is not the only instance in the paper of virus isolation, so it simply does not have the importance in the context of the overall paper that ORI ascribed to it. The main complaint of ORI's witnesses was that the pooling technique used in infecting the parental cell line was not good science. Contrary to what ORI argued, however, the paragraph in question does not hide the fact that more than one patient sample was used to infect the parental T-cell line. We find it highly unlikely that Dr. Popovic would have revealed that he used a less than ideal technique and then chosen an ambiguous at best method of misrepresenting the logic of that technique.

SECOND, ORI FOUND THAT SIX "ND" ENTRIES IN TABLES 1 AND 2 IN THE PAPER FALSELY REPORTED THE EXPERIMENTAL RESULTS, GIVEN THE DEFINITION "ND, NOT DONE" (WHICH APPEARS IN FINE PRINT IN THE MIDDLE OF THE LEGEND TO TABLE 1). ORI interpreted "not done" as meaning "not performed" (in the sense of not even attempted). ORI concluded from the laboratory records that the experiments reported as "ND" had been performed.

2. We conclude that ORI's second finding is not supported by a preponderance of the evidence, for the following reasons:

o The evidence shows that both ND and "not done" are subject to differing interpretations, some of which would accurately represent the results of the reported experiments. ORI did not substantiate its view that "not done" can only mean "not performed."

o Persuasive testimony by expert retrovirologists corroborates Dr. Popovic's testimony that his use of "ND" involved a reasonable judgment of how to report the experimental results. This expert testimony also showed that reporting the entries exactly as they appeared in the laboratory records would not have made any difference in how a retrovirologist would evaluate the data in the tables.

o The expert testimony on which ORI relied was based on reading the technician's notes in a way which is not consistent with her testimony on what she meant, which fails to consider the nature of the experiments reported, and which fails to consider other experimental results. These other results, of parallel tests, contradict ORI's expert advisors' reading of the laboratory notes to mean that there was no virus expression.

ORI'S THIRD FINDING WAS THAT A 10% ENTRY IN TABLE 1 WAS FALSE BECAUSE IT WAS INCONSISTENT WITH THE TECHNICIAN'S RECORDED READING OF ASSAY RESULTS ON A SLIDE AND BECAUSE THE 10% DID NOT APPEAR IN ANY LABORATORY RECORDS THAT WERE AVAILABLE IN 1990 WHEN THE INVESTIGATION BEGAN.

3. We conclude that ORI's third finding is not supported by a preponderance of the evidence, for the following reasons:

o ORI's finding on the 10% entry is also based on a misreading -- in this instance a misreading of both the technician's notes "very few cells positive for rabbit antibody" and a written explanation the technician gave during the investigation. The technician's testimony shows that ORI's expert, in determining that likely 100% of the cells left on the slide were positive, had misunderstood the technician's explanation of what she did. Moreover, the evidence shows that a 100% value is unlikely, since the reading for the same culture eight days later was less than that.

o Persuasive evidence shows that Dr. Popovic also read the slide and that the 10% is likely the true value. ORI

presented no evidence that would indicate the 10% is an impossible, or even an unlikely value.

o **The absence of a written note for the 10% is not significant, in light of all of the circumstances here.** These circumstances include the fact that a number of years had passed since the experiments were performed. ORI failed to establish any motive for Dr. Popovic to have fabricated this one insignificant data point.

4. We conclude that ORI did not prove by a preponderance of the evidence that there was any pattern of conduct to falsify methods and data.

o **Finally, contrary to what ORI and its scientific advisors found, we do not find here a pattern of conduct of falsifying methods or data to make the experiments reported in the Science paper look more rigorous than they in fact were.** ORI established at most two ambiguities (rather than untruths) in the paper: the "first shown" in the disputed sentence and the "not done" in the legend to Table 1. While we recognize that a researcher deliberately intending to mislead a reader might cleverly choose to do so through introduction of subtle ambiguities, we conclude that ORI did not establish such a scenario is likely here:

- o ORI did not establish that Dr. Popovic's English skills were sufficient so that he would have understood the ways in which the words "first shown" and "not done" might have been misleading to a reader who interpreted them as ORI did.
- o ORI did not establish that Dr. Popovic drafted the "first shown" language or retained it in the paper after recognizing an ambiguity. Since he honestly disclosed in the paper that he used fluids from more than one patient to infect the parental T-cell line, we think it unlikely that he then in a calculated way tried to enhance the logic of doing so.
- o ORI's advisors were under the impression that the effect of each of the ND entries was to slant the data toward the hypothesis of the paper and to mislead the reader about the rigorousness of the experiments. The evidence does not support such a conclusion. None of the data points at issue (one of which was recorded as positive in the technician's notebook) had any significance to the conclusions of the paper. Persuasive testimony from retrovirologists -- representing

the researchers who potentially would be the most critical readers of the paper -- was that they would not have evaluated the experiment any differently if Dr. Popovic had reported these results exactly as they appeared in the notebook. On the other hand, the testimony from the non-retrovirologists supports the reasonableness of Dr. Popovic's judgment that doing this would have been misleading to others.

LEGAL FRAMEWORK

The Department of Health and Human Services has the discretionary authority to protect the integrity of research it funds by taking administrative actions against those who have engaged in scientific misconduct. In 1992, the Departmental Appeals Board, in the Office of the Secretary, was given responsibility for hearing appeals from findings of scientific misconduct made by ORI. See 57 Fed. Reg. 53,125 (1992). Under the applicable guidelines, a Research Integrity Adjudications Panel is appointed to decide each appeal.²

The guidelines provide for a de novo review. What this means is that our decision is not a review of what ORI did during its investigation or whether what ORI found was reasonable based on the evidence ORI considered. Rather, we held a 12-day evidentiary hearing during which both sides had an opportunity to present testimony from witnesses and documentary exhibits. This hearing was Dr. Popovic's first opportunity to confront and cross-examine witnesses against him and to test the expert opinions on which ORI relied.³ Our decision is based solely on the evidence admitted into the record before us.

The purpose of this proceeding was not to revisit all of the issues addressed in the ORI Report. Under the guidelines, the Panel is to determine whether ORI proved

² Although the guidelines permit appointment of a scientist to the panel, neither party requested that a scientist be appointed to the panel in this case.

³ See Appendix C for a brief description of each witnesses' background, the area of expertise (if any) in which they were qualified at the hearing, and the party for whom they testified.

the findings of scientific misconduct which ORI made, and which were appealed, and to determine the appropriateness of the proposed administrative action. This narrowed the case considerably from what was involved earlier in the investigation.

The guidelines require ORI to prove scientific misconduct by a preponderance of the evidence. This means evidence that is more convincing than the opposing evidence and shows as a whole that misconduct was more probable than not.

In this decision, we evaluate the evidence presented against the regulatory definition of scientific misconduct published in 1989, and find it lacking. That definition states:

Misconduct or Misconduct in Science means fabrication, falsification, plagiarism or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting or reporting research. It does not include honest error or honest differences in interpretations or judgments of data.

42 C.F.R. § 50.102.

There was considerable controversy in this case over whether this definition is properly applied to intramural research conducted in 1983-84, such as the research at issue here. However, since ORI failed to present evidence adequate to show that the 1989 regulatory definition was met, and since there was no evidence presented to suggest any more stringent earlier standard, we do not need to resolve this controversy or to decide exactly what would have been understood in 1983-84 to be scientific misconduct in intramural research.⁴

⁴ Early in these proceedings, Dr. Popovic filed a motion to dismiss raising substantial questions concerning the fairness of applying the 1989 definition, which established requirements for extramural research, to intramural research conducted in 1983-84. We ruled that ORI had to prove both that any reasonable researcher in Dr. Popovic's position would have considered Dr. Popovic's conduct to be scientific misconduct at the time and that the 1989 definition was met. ORI presented extensive testimony at the hearing in an effort to prove what would have constituted scientific misconduct in 1983-84. Most of this evidence was conclusory and merely
(continued...)

ORI argued here that to meet the 1989 definition of scientific misconduct, ORI did not need to prove that Dr. Popovic had an intent to deceive. ORI relied in part on what it said was the legal definition of "falsification" (but in fact was the legal definition of "false"). Black's Law Dictionary (5th Ed. 1979 at 540, cited by ORI) indicates that the term "false" may sometimes be used to encompass a thing that is untrue by mistake or accident, with no intent to deceive. ORI's argument begs the question of whether the term "falsification" as used in the regulatory definition of misconduct encompasses mere mistaken or accidental untruths. The regulatory definition itself indicates otherwise since it specifically excludes "honest error or honest differences in interpretations or judgments of data."

Moreover, ORI's argument that scientific misconduct encompasses unintentional conduct is contrary to a statement in the 1990 Guidelines for the Conduct of Research at NIH. That statement refers to scientific misconduct as "fabrication, falsification, plagiarism, or other practices motivated by intent to deceive." Exhibit (Ex.) P-20 at 15. This interpretation is consistent with reading the exclusion of "honest error or honest differences in opinion" as meaning that the 1989 definition encompasses as falsification only conduct intended to deceive.⁵

In any event, while we discuss below why we conclude that ORI did not prove intentional deception here, we also discuss why we conclude that ORI did not prove by a preponderance of the evidence that the disputed statements or data were untrue at all. Thus, even if we agreed with ORI (which we do not) that unintentional errors in insignificant details in a paper would constitute scientific misconduct under the 1989 definition, we would not reach a different result here.

⁴ (...continued)

went to undisputed general propositions, such as that intentional falsification of scientific data and methods has never been acceptable.

⁵ Dr. Richards, one of ORI's scientific advisors, testified that "honest error" is not a basis for sanction -- "honest meaning that at the time the manuscript was submitted, it was thought to be correct." Panel Hearing Transcript (Tr.) at 467; see also Tr. at 1127 (Woolf); Tr. at 1064 (Berns); Tr. at 1247 (Huth).

FACTUAL FRAMEWORK

We discuss here the factual framework needed to help the reader understand the context of this dispute.⁶

A. THE STATUS OF AIDS RESEARCH IN THE EARLY 1980'S

In the early part of 1981, information on AIDS was limited. The initial cases recognized a severe immunodeficiency in some homosexual men. Later it was learned that AIDS was occurring in other populations such as hemophiliacs and intravenous drug users. Prior to the publication of the Popovic Science paper, AIDS was recognized as a fatal disease which was epidemic. Scientists and clinicians had considerable questions and concerns about the cause of this disease. By mid-1983, the scientific community recognized that AIDS was a transmissible agent and that the "pathogen was in the blood supply." Tr. at 1965, 1968-69 (Blattner). People were developing AIDS as a result of blood transfusions, causing anxiety in the medical community and in the public at large. Consequently, there was strong motivation to find the cause of AIDS in order to attempt to save lives and protect the blood supply.

Working with tissue and blood samples from patients with AIDS at this time was considered dangerous. Many laboratories in this country and elsewhere would not permit clinical specimens from AIDS patients in the laboratory. Nonetheless, scientists around the world embarked on a concentrated, intense search for the causative agent of this disease.

⁶ The factual framework here is derived from stipulations entered into by the parties and from testimony of Drs. Blattner (Tr. at 1964-64, 1967-69, 1977, 1986), Gartner (Tr. at 1797-98, 1806-07, 1817-18, 1836-39, 1890), Popovic (Tr. at 2258, 2260-63), Sodroski (Tr. at 615-16, 646-50, 684-85, 687, 700-01, 733-37, 782), Svoboda (Tr. at 1943-44, 1947-51), and Gallo (Tr. at 2018-21, 2087, 2090-91). Much of this testimony was addressed in proposed findings of fact supported by citations to the record submitted by Dr. Popovic to which ORI did not directly respond with any citations to the record contrary to our factual statements here. Therefore, we do not consider these factual matters in dispute.

Numerous theories were being circulated, such as that a fungus, a common virus, or homosexual activities were the cause of AIDS. NIH announced a month or two before the Science paper at issue here was published that a fungus was the cause of AIDS. In late 1982, Dr. Robert Gallo, chief of the Laboratory of Tumor Cell Biology (LTCB), NIH, and Dr. Max Essex, from Harvard, began to theorize about the cause of AIDS and whether it might be caused by a human retrovirus.⁷ Little by little the LTCB got into AIDS research. By mid-1983 the research efforts in the LTCB were intense and by mid-1984, AIDS dominated that laboratory's research.

Dr. Sodroski testified that prior to the publication of the Science papers, there was skepticism in the scientific community that a retrovirus was the cause of AIDS. Dr. Sodroski indicated that the four Science papers resulting from the LTCB research reported multiple isolations, showed the virus established in a stable cell line for diagnosis, and provided serological data showing that there was a high percentage of people in the at-risk group or who had AIDS that had antibodies to this virus. Dr. Sodroski stated that as a result of the Science papers, he, as a retrovirologist, became convinced that a retrovirus was the cause of AIDS. Dr. Blattner, an epidemiologist actively involved since the early 1980s in AIDS research, stated that the Science papers proved unequivocally that the cause of AIDS was a human retrovirus. Tr. at 1986.

B. DR. POPOVIC AND HIS WORK

Dr. Popovic was trained as a physician in Czechoslovakia and in 1971 received a Ph.D. in cytopathology from the Cancer Research Institute, Slovak Academy, in Bratislava, Czechoslovakia. His postdoctoral training in cell biology was at Wallenberg Laboratory, University of Uppsala (Sweden).

⁷ A retrovirus is a virus whose genetic information is encoded in ribonucleic acid (RNA). A retrovirus reproduces by creating a deoxyribonucleic acid (DNA) copy of its RNA. HIV, the name by which the AIDS virus is now known, is a retrovirus. See Glossary of scientific terms agreed to by the parties at 3 and 5.

Dr. Popovic is a cell biologist.⁸ He began his scientific career in Czechoslovakia under the tutelage of Professor Jan Svoboda, considered one of the "Fathers of Retrovirology." Tr. at 1836-37 (Gartner). Together they worked with the avian sarcoma virus.

Dr. Popovic initially came to the LTCB in 1980 as an American Cancer Society Fellow and worked initially on HTLV-I, a retrovirus responsible for human T-cell lymphoma leukemia. There were few people at that time who were involved in the study of human retrovirology. During 1982-1984, Dr. Popovic was a Visiting Associate in the LTCB, and then from 1984-1989, he was a Visiting Scientist at the LTCB. Dr. Popovic, who became a United States citizen in 1984, has published approximately 163 papers during his career as a research scientist and has been listed as first author on 31 of those papers.

Dr. Popovic, because of his belief that the cause of AIDS might be a human retrovirus, used the techniques he learned in Czechoslovakia to isolate and grow a new retrovirus. The work in the LTCB with the first human retrovirus isolates, HTLV-I and HTLV-II, in the 1970s and 1980s provided invaluable background information for the later work with AIDS. This work provided information on "ways to detect [human retroviruses] efficiently, ways to grow the right kinds of cells, and . . . to know that T-lymphocytes were the right kinds of cells to grow." Tr. at 736-37 (Sodroski).

Since there was no conclusive evidence that a retrovirus was the causative agent of AIDS, Dr. Popovic's work on AIDS involved a search for an unknown virus. Searching for an unknown virus is not like working with a known virus. It involves searching for clues much like detective work or attempting to put pieces of a large puzzle together. It involves using a variety of laboratory methods to first determine whether a virus is

⁸ The study of retrovirology is a subspeciality of virology; the process by which a retrovirus replicates is different from the usual process of virus replication. Moreover, within the field of virology and the subspeciality of retrovirology, there is a further specialization among those working in these areas: some scientists are cell biologists who study the virus in the context of the total living cell and attempt to detect, isolate, and propagate individual viruses or retroviruses; others are molecular biologists who concentrate on the subcomponents of viruses such as DNA, RNA, and nucleic acid.

present and using other methods to isolate that virus and propagate it.

Dr. Sodroski indicated that in most body fluids from infected individuals, the amount of starting material that is infectious is very small. Thus, a scientist wants to be able to first propagate the virus by making the virus make more of itself in tissue culture, because it is easier to detect virus once there are a lot of infected cells making a lot of viral protein. However, the major difficulty with the AIDS virus is that it is cytopathic, meaning it kills the target cells used to establish a culture, and it will grow in some target cells and not in others. To overcome these obstacles and succeed in growing such a virus requires not only science, but "art" and probably even "luck", or a "green thumb." Tr. at 782 (Sodroski); Tr. at 1977 (Blattner).

C. WHAT THE SCIENCE PAPER WAS ABOUT

We have attached as Appendix A of this decision the Science paper at issue. As explained in the abstract to the paper, the paper reported on development of a "cell system" for the "reproducible detection of human T-lymphotropic retroviruses (HTLV family) from patients with the acquired immunodeficiency syndrome (AIDS) or with signs or symptoms that frequently precede AIDS (pre-AIDS)." The cells were described as "specific clones from a permissive human neoplastic T-cell line," some of which "permanently grow and continuously produce large amounts of virus after infection with cytopathic (HTLV-III) variants of these viruses." The abstract explained that the significance of the reported research is that the cell system "opens the way to the routine detection of HTLV-III and related cytopathic variants of HTLV in patients" and "provides large amounts of virus for detailed molecular and immunological analyses." Ex. H-5 at 497.

The paper focuses on experimental results for those clones of the permissive cell line which were found to permanently grow and continuously produce large amounts of virus. One paragraph of the three-page paper discusses the preliminary infection of the parental T-cell line (from which the clones were developed). Dr. Popovic's original handwritten draft of the paper did not discuss this infection at all. This infection was discussed only because of a later decision to develop an AIDS test using the variant, later designated HTLV-IIIB, growing on one of the clones (designated H9) after it was infected by exposure to concentrated virus from the

infected parental T-cell line. The paper also describes, in somewhat greater detail, the infection of the cell clones with isolates from individual patients.

The authors of the paper do not purport to have isolated one virus (or one variant of a virus) as the cause of AIDS. Instead, the abstract refers to cytopathic variants of viruses. The paper itself states: "These new HTLV isolates are collectively designated HTLV-III, although it is not yet proved that they are identical." Ex. H-5 at 498. The paper reports a number of different isolates.⁹

Experimental results reported in the tables in the paper are results of infection of the clones with the virus variant produced by the parental T-cell line, at 6 and 14 days after infection, and with individual patient isolates.

Next we turn to our detailed analysis of each of the three major findings of scientific misconduct.

DETAILED ANALYSIS

A. THE DISPUTED SENTENCE

The key sentence at issue appears in a paragraph describing how the parental cell line was infected, prior to the cloning and infecting of the clones. We reproduce here most of the first four sentences of that paragraph to preserve the immediate context in which the allegedly false sentence appears:

⁹ ORI seemed to ignore this point, as though the paper (together with the papers published at the same time) were claiming that AIDS was caused by HTLV-III~~B~~ (a variant designation which is not even mentioned in the paper). The HTLV-III~~B~~ variant, as grown on clone H9, became the basis for the AIDS blood test, and is the variant which has a striking molecular similarity with a contaminant of the LAV variant French researchers had reported on and allegedly sent to the LTCB. Unrebutted testimony here establishes that Dr. Popovic had advocated using an individual patient isolate, and that the decision to use the HTLV-III~~B~~ variant was made by others on the basis that its growth was more advanced.

The cell line HT was tested for HTLV before being infected in vitro and was negative by all criteria including lack of proviral sequences (32). Continuous production of HTLV-III was obtained after repeated exposure of parental HT cells . . . to concentrated culture fluids harvested from short-term cultures of T cells (grown with TCGF) obtained from patients with AIDS or pre-AIDS. The concentrated fluids were first shown to contain particle-associated RT. When cell proliferation declined, usually 10 to 20 days after exposure to the culture fluids, the fresh (uninfected) HT cells were added to the cultures. Culture fluids from the infected parental cell line were positive for particulate RT activity,

Ex. H-5 at 498 (emphasis added; reference omitted).¹⁰

Dr. Popovic's testimony, and his notebooks show, that he: 1) exposed the parental T-cell line on November 15, 1983 to concentrated culture fluid harvested from cultures of three patients' primary cells; 2) exposed the parental cell line on November 22, 1983 to concentrated culture fluid from the same three patients' cultures; and 3) exposed the parental cell line on January 2, 1984 to concentrated culture fluid from seven more patients' cultures. Ex. H-19 at 33, 34, 44; Ex. H-157 at 29-35; Tr. at 2397-98.¹¹

¹⁰ Reverse transcriptase (RT) is an enzyme protein found in retroviruses. Glossary at 5. Retroviruses use reverse transcription to convert their genetic material (RNA) into DNA in the process of producing more virus. Tr. at 642-43 (Sodroski); see also Tr. at 1799 (Gartner). The LTCB had developed an assay to detect RT. A positive RT is a good indication that a retrovirus is present, but a negative RT does not mean that a retrovirus is not present; virus expression might simply be below the level of detection. Tr. at 1800-07 (Gartner).

¹¹ ORI's report accepted this scenario as true. At the hearing, however, ORI raised allegations for the first time concerning whether the pool existed and whether the notebooks were authentic. We agree with Dr. Popovic that ORI's timing and manner of raising these allegations were unfair since it did not allow adequate opportunity for Dr. Popovic to prepare a response. We have nonetheless discussed these allegations below since the record as developed -- including testimony by ORI's own witnesses -- calls these allegations into question
(continued...)

ORI's finding that the underlined sentence is false was based on ORI's reading of that sentence as meaning that Dr. Popovic tested individual patient samples from each of the ten patients for RT activity, before "pooling" those samples to infect the cell line, and showed that all of them were positive for RT activity. See, e.g., ORI post-hearing br. at 46-49. It is undisputed that each of the ten individual patient samples was not found positive for RT activity before being used to infect the cell line. See Tr. at 2302-04. Dr. Popovic testified, however, that after he first pooled and then concentrated the fluids he had harvested from individual patient cultures, he sent part of the pooled concentrated culture fluid for RT analysis at the same time as he used another part of the concentrated fluid to infect the cell line; he said that he had obtained the results (which were positive) from Dr. M.G. Sarngadharan, after exposing the cell line. Tr. at 2498.

ORI alleged that there were two falsifications in the sentence: "one that it was not first shown; and two, that [RT results for individual patient samples] were not all positive." Tr. at 235. ORI presented evidence which it said showed that many of the ten individual samples tested negative for RT, that, at most, only one of the ten samples was tested and shown positive for RT before it was pooled, and that only six of the ten samples contained any AIDS virus.¹²

We conclude that ORI has not proved by a preponderance of the evidence its finding that Dr. Popovic falsified the disputed sentence, for the following reasons:

- ORI's finding depends on a reading of the disputed sentence which is not the only reasonable reading. ORI's reading that "concentrated fluids" means individual patient samples ignores unrebutted testimony and other evidence that the fluids from the patient samples were first pooled and then

¹¹ (...continued)

and since they might otherwise unfairly harm Dr. Popovic's reputation, having been raised in a public forum.

¹² The evidence on the RT tests was from the notebooks of Dr. Prem Sarin at the LTCB. The evidence on whether the samples contained AIDS virus was from polymerase chain reaction (PCR) analysis on aliquots of patient samples provided by ORI to Roche Diagnostics as part of the ORI investigation.

concentrated. Moreover, in context, the "first" can reasonably be read as intended to convey that the RT activity was associated with the concentrated patient fluids (and therefore a virus had been transmitted from the fluids to the cell line).

- ORI's reliance on its experts' opinions on the meaning of the sentence is misplaced since, for the most part, the experts did not independently determine the meaning of the sentence. Their testimony as a whole supports a conclusion that, in context, the statement is merely ambiguous.
- We find Dr. Popovic's testimony about what he in fact did to be credible since that testimony is consistent with the laboratory notebooks, is corroborated by others' testimony, and is unrebutted.
- ORI did not show either that Dr. Popovic added the sentence in question or that in the editing process he was made aware of the addition of the sentence and should have known it may have been misinterpreted.
- ORI overrated the significance of the sentence in arguing that Dr. Popovic had a motive to falsify it. ORI did not establish that the paragraph was the key methodological section of the paper, nor that Dr. Popovic would have viewed what he in fact did as illogical and lied about it to make his experiment appear more rigorous.

1. ORI misread the sentence.

In our view, the greatest weakness in ORI's case is that it is dependent on reading the disputed sentence a particular way, which is not the only reasonable reading of the sentence. Indeed, ORI's view that the sentence falsely states that each individual patient sample was tested for RT activity before pooling and shown positive ignores the context in which the sentence appears.

The context refers to "repeated exposure" (more than one exposure) of the parental T-cells to "concentrated culture fluids" (more than one fluid) harvested from short-term cultures obtained from "patients with AIDS or pre-AIDS" (more than one patient). ORI reads the plural "fluids" as referring to fluids from individual patient samples because it assumes that the fluids were concentrated before they were "pooled." However, ORI provided no evidence to support that assumption. The wording of the sentence is not inconsistent with RT

testing of different fluids obtained after patient cultures were first pooled and then concentrated and used for different exposures (which is what Dr. Popovic has consistently stated that he did). Indeed, if the writer intended to suggest testing of each individual patient culture either before pooling or before exposing the cell line, one would expect different wording (for example, "Each patient culture tested positive for RT activity before the exposure.").

Similarly, ORI's view that the disputed sentence is false because the tests for RT activity were performed after the cell line was infected is contingent on reading of the word "first" as establishing a priority in the timing of RT testing compared to the timing of infecting the cell line.¹³ In context, however, the "first" can reasonably be read as having a different purpose. Two sentences later the reader learns that culture fluids from the infected cell line were tested for RT activity after infection. Thus, the significance of the "first" in the disputed sentence can reasonably be seen as establishing a priority in the RT activity as occurring in the concentrated culture fluids harvested from the patient cultures before those fluids were used to infect the cell line. It is not unambiguously clear that it means that the RT tests were performed before the cell line was exposed to the concentrated culture fluids.

ORI did not establish that the timing of the tests for RT activity in the concentrated culture fluids relative to the timing of the infection would have any significance critical to the paper's conclusions.¹⁴ On the other

¹³ While the word "first" may suggest a priority in time, this is not its only meaning. One part of the definition of the word "first" is "before any or some other person or thing (as in time, space, rank, or importance): as the first thing to be mentioned"
" Webster's Third New International Dictionary at 856.

¹⁴ As discussed below, ORI relied on testimony that it would be "logical" to test for RT activity before pooling samples and using them to infect the pool (because positive RT would indicate presence of the virus). Dr. Popovic presented persuasive evidence, however, that given his training and practices, he would not have viewed what he in fact did as illogical, even if it was not optimal. In any event, even if it would have been more logical to test for RT first, ORI presented no evidence that reporting that the tests were performed on
(continued...)

hand, tests which would indicate that RT activity was present in the patient fluids and not in the cell line are significant to the paper's conclusions. The paper needed to establish that the retrovirus was transmitted to the cell line from the patient culture fluids and was not already present in the cell line. Indeed, the paragraph in question begins by referring to tests which indicated that the cell line was negative for HTLV before infection.¹⁵

That one possible intent of the word "first" was merely to indicate that RT activity was present in the fluids used to infect the cell line is supported by a comparison of drafts seven and eight of the Science paper. Draft seven contains the following sentence:

Continuous production of HTLV-III was obtained after repeated exposure of parental HT cells . . . to concentrated culture fluids positive for particulate reverse transcriptase (RT), which was harvested from short term cultured T-cells originated from patients with lymphadenopathy and AIDS.

Ex. H-12 at 6.

This sentence does not contain the words "first shown." The editorial change which appears on draft eight and which created the disputed sentence, considered in context, clarifies and emphasizes evidence that the retrovirus was present in the concentrated culture fluids used to infect the cell line. The most likely reason for emphasizing this evidence is that it supports the overall conclusion that a retrovirus had been transmitted to the cell line from the patient fluids.

¹⁴ (...continued)

part of each of the three concentrated culture fluids after another part of each was used to infect the cell line would have undercut the conclusions of the article.

¹⁵ One of ORI's experts, Dr. Martin, testified that "the first sentence basically says that by the criteria and tests that were available . . . the recipient cell was clean, that is to say it didn't contain any other virus." Tr. at 1324. He explained that this was important "because if the recipient cell contains . . . a virus, then what would be . . . isolated at the end of the procedure, would be this so-called contaminant virus and not the real cause of the . . . disease." Tr. at 1325.

In sum, ORI's reading of the disputed sentence (on which ORI's allegation depends) fails to consider the sentence in light of the context, purpose, and wording of the paragraph as a whole. The disputed sentence, while ambiguous, can reasonably be read as consistent with what the evidence shows, in fact, occurred. Dr. Popovic conceded during the ORI investigation, after ORI had pointed out that it was reading the "first" to mean before the pooling and infection, that the sentence (as interpreted by ORI) could be seen as imprecise because RT positivity of the fluids was not "shown" until after the pooling and infection. But the fact that the sentence could reasonably be read another way is important, for two reasons.

First, if Dr. Popovic were intentionally trying to mislead the reader into believing that each of the individual patient samples had tested positive for RT activity before being pooled, one would have expected him to do it in a more direct and unambiguous way. Second, ORI took the position that, even if Dr. Popovic did not add the "first shown" sentence, he should be found guilty of scientific misconduct because he had the responsibility to change the sentence to ensure its accuracy. The fact that the sentence is ambiguous -- and that the one word "first" might add imprecision if read a particular way -- supports our conclusion that failure to change the sentence did not amount to a falsification. This is one reason why (particularly in light of Dr. Popovic's English-speaking abilities at the time) we find credible Dr. Popovic's testimony that, if he saw this change when editing the galley proofs of the paper, it did not impress him as false.

2. The expert testimony does not establish that the sentence is false.

ORI argued that we should find the disputed sentence to be false because testimony from its experts supports its view that the disputed sentence should be interpreted to mean that individual patient samples were tested and shown RT positive before the pooling. But, in fact, the experts' testimony was not dispositively supportive.

ORI did not argue that the expert testimony showed that the plain wording of the sentence makes it subject to only one reasonable interpretation. Nor does the cited testimony support a conclusion that ORI's is the only reasonable interpretation.

We found the testimony on this sentence by the scientific advisors who had been involved in ORI's investigation

(Drs. Richards, Berns, and Schaffer) to be either irrelevant or unpersuasive -- in spite of these experts' impressive credentials, for the following reasons:

- Based on their testimony as a whole, as well as their own descriptions of their role in the investigation, we find that these advisors did not form their opinions independently, after consideration of all of the relevant evidence. See, e.g., Ex. H-73 at 1; Tr. at 468-70, 481, 512 (Richards); Tr. at 1042, 1062 (Berns); Tr. at 1578-80 (Schaffer). They had reached conclusions based on assumptions derived from how ORI investigators presented the issues to them and based on partial evidence. They appeared unable to reevaluate those conclusions when those assumptions were questioned -- perhaps due to their involvement in the investigation of the origin of HTLV-III_B, frustration over the difficulties of resolving this question, and association with the ORI findings. See, e.g., Tr. at 1639-44; 1660-65 (Schaffer).
- None of these experts appeared to have carefully examined the language and context of the disputed sentence, or to have independently tested it against the record. During their direct testimony on the sentence, Drs. Richards and Schaffer each conclusorily testified that the sentence was false because it "says" or "said" that the individual patient samples had been shown to be RT positive before they were used to infect the cell line. Tr. at 498-500 (Richards); Tr. at 1491-92 (Schaffer). They appeared unaware of possible ambiguities. For example, Dr. Schaffer's explanation of her interpretation assumed that each concentrated culture fluid was from an individual patient. Tr. at 1502-03; 1505-06. Dr. Berns appeared to be under the impression that Dr. Popovic had conceded that the sentence falsely stated that all of the individual patient samples had been tested before being pooled. Tr. at 1045, 1064. In other words, the opinions these experts provided were based on assumptions about what the sentence meant, rather than on the wording, context, or underlying facts.
- When Dr. Schaffer's attention was focused on the exact language in the paper, she acknowledged that it was ambiguous. Tr. at 1660-62. Dr. Richards admitted that, in reading the sentence to say that the RTs were all done and were all positive, he did not know when the samples became concentrated fluids. Tr. at 500.
- In some instances, these experts drew unreasonable inferences from non-scientific evidence. For example,