Department of Health and Human Services

DEPARTMENTAL APPEALS BOARD

Research Integrity Adjudications Panel

SUBJECT: Kimon J. Angelides, Ph.D.
Docket No. A-97-98
Decision No. 1677

DATE: February 5, 1999

DECISION

On April 8, 1997, Kimon J. Angelides, Ph.D., appealed to the Research Integrity Adjudications Panel (RIAP, Panel) eleven charges of scientific misconduct brought against him by the Office of Research Integrity (ORI). Dr. Angelides was charged with intentionally falsifying data and misrepresenting research results in grant applications submitted to the National Institutes of Health (NIH) and in five papers published while he ran a laboratory at the Baylor College of Medicine (Baylor). A Panel of three members was appointed by the Chair of the Departmental Appeals Board, in accordance with the guidelines of the RIAP, to hear this appeal.

The Panel consisted of M. Terry Johnson (Presiding Panel Member), Donald F. Garrett, and Regis B. Kelly, Ph.D. Ms. Johnson and Mr. Garrett are Members of the Departmental Appeals Board. Dr. Kelly is Chair of the Department of Biochemistry and Biophysics at the University of California at San Francisco and was appointed to serve on this Panel upon the joint recommendation of the parties. See Appointment Letter (Aug. 27, 1997). The Panel conducted an independent proceeding, including a full in-person hearing and careful review of voluminous exhibits and original primary data and notebooks. Based on its de novo review, the Panel concluded that Dr. Angelides committed scientific misconduct, as explained below. The Panel further determined that the administrative actions proposed by ORI were justified, and recommended that Dr. Angelides be debarred from eligibility for federal grants and contracts for a period of five years. The factual findings, legal analyses, and ultimate conclusions on which this determination and recommendation is based are set forth in the body of this decision.

PREAMBLE

I. Summary

Dr. Angelides has litigated this case not so much as a matter of a scientist defending against government charges as one of scientist against scientist. For the most part, he did not dispute that the data at issue were misreported. Dr. Angelides sought a total of over four million dollars in limited federal research funding in the grant applications in which the Panel has concluded that

he intentionally committed scientific misconduct. As principal investigator, Dr. Angelides undertook personal responsibility to base each application on truthful information. Yet, in each instance where suspicions arose that he had not honestly presented his laboratory's research results in different grant applications or published papers, he in turn accused his junior laboratory members of having misled him. See, e.g., Record Exs. 29, 32, 36, and 37. The Panel carefully evaluated each of these instances and found that Dr. Angelides's accusations against other researchers were unsubstantiated.

Most of the scientific misconduct established in the record consisted of Dr. Angelides reporting falsely primary data as the successful results of experiments that either had not been successful, or, in many cases, had not even been attempted. Forty figures in five journal articles and five grants were falsified; in some instances the same primary data were reused without changes, while in others the false identification of primary data was changed to a different false identification. Some falsifications were relatively straightforward, such as overstating the number and variety of certain reagents produced by the laboratory or attempting to enhance the perception of the specificity of an antibody. Many misrepresentations, such as claims respecting the work of the laboratory's molecular biologist, were exaggerations of the accomplishments of Dr. Angelides's laboratory in projects which had in fact met with little success. All these falsifications tended to give Dr. Angelides an unfair advantage over honest scientists in competing for funds and for publication opportunities.

When the charges of falsification first surfaced, Dr. Angelides took the position that all the problems resulted from two dishonest, disgruntled former members of his laboratory whose work had led to "unpublished, false, and irreproducible data." Record Ex. 32, at 2; see also Record Ex. 34, at 1. As additional instances of false reporting of data and research results were uncovered, however, it became evident that data in which these two researchers had no role were also falsely reported and that misrepresentations occurred over many years even when they were not in the laboratory. The alternative explanations offered by Dr. Angelides for how so many different members of his laboratory could have misled him in so many ways over so many years became increasingly strained and implausible. The Panel found Dr. Angelides's pattern of blaming and accusing so many others, especially junior laboratory members for whom he had served as a mentor, to be disturbing and to demonstrate a troubling failure to take responsibility for the consequences of his own actions.

Moreover, when the Sub-Committee assigned by Baylor to review these cross-charges concluded that Dr. Angelides was solely responsible for the misrepresentations involved, Dr. Angelides responded by attacking the Baylor Sub-Committee for falsifying and fabricating data itself, tampering with evidence, intimidating witnesses, and lacking adequate expertise to understand his defenses. See, e.g., Angelides (Ang.) Resp. to Baylor Report passim; Ang. Post-Hearing Brief (Ang. Br.) at 21-23, 215, n.168. When an Appellate Committee at Baylor concurred with the final report of the Baylor Sub-Committee, Dr. Angelides made similar personal attacks on the members of that committee, including a member whose appointment Dr. Angelides himself had urged. In the course of these proceedings, a number of scientists who worked in Dr. Angelides's

laboratory at various times, many of whom initially supported him and believed that he would not have falsified data, testified that, after learning more about the evidence against him, they had reluctantly come to the conclusion that the charges were substantiated. Dr. Angelides's response was to accuse them of having been corrupted by Baylor or ORI. Ang. Br. at 7. He denigrated his former collaborators who testified before the Panel as lacking "any knowledge about the scientific issues." Ang. Br. at 14.

Although testimony presented to the Panel was often conflicting, the conflict was between Dr. Angelides and all of his colleagues, whose testimony was consistent with each other. The Panel also compared the testimony with the written record, most particularly the laboratory notebooks of those involved. Although record-keeping was by no means exemplary, in almost every case the recollections of Dr. Angelides's colleagues matched the records, while the claims of Dr. Angelides did not. Furthermore, the recollections of the colleagues made sense, whereas the scenarios proposed by Dr. Angelides did not. The Panel did not find it likely that the young investigators would have reported major (though falsified) discoveries to Dr. Angelides and yet he would not have become suspicious when they did not share these achievements with others or present their data at group meetings. Further, the Panel found it implausible that Dr. Angelides did not question why one of these investigators then left graduate school as a failure and the other dropped what would have been a spectacular project. Nor did the Panel find it believable that two of these investigators would collude to assemble a false figure when they were no longer in the laboratory.

The Panel also noted that the falsifications consistently appeared in contexts in which they would be extremely difficult to detect. For example, data were misused most often after the experimentalist had departed the laboratory (leaving the data in Dr. Angelides's possession and control), in grant applications that would not be reviewed by those who had reputedly generated the data, and in papers on which Dr. Angelides was the only author listed from his laboratory. The data on gel electrophoresis are by their nature particularly easy to falsify, and cannot be checked without intensive study of the primary data. The data in grants are protected from scrutiny and verification by the confidentiality of the review process. The Panel repeatedly found that Dr. Angelides excluded the actual experimentalists from the process of drafting and reviewing the grant applications and manuscripts at issue, so that they did not have the opportunity to discover or correct the false presentation of their data or research results. Conclusions that are hard to verify are those that most depend on trust in the investigator. The Panel found that Dr. Angelides attempted to misuse that trust.

Dr. Angelides characterized this as a situation where all of a scientist's output had been meticulously searched for errors long after the fact, a scrutiny which might make any busy scientist fear that retrospective examination would subject them to penalties despite a long career in which no questions had been raised about their integrity. However, this picture does not correspond with the evidence in the record before us. What the Panel found here was not honest error, not disputes in interpretation of data, not preliminary results that later proved overly optimistic, not even carelessness, but rather intentional and conscious fraud. Honesty is key to

the scientific process and requires trust among scientists, precisely because a thorough, independent review of the original record such as occurred here can and should rarely be undertaken. However, by intentionally presenting data that he knew were not what he claimed they were and by intentionally misrepresenting the state of progress on aspects of his research, Dr. Angelides unfairly sought to advantage himself in seeking competitive funding and opportunities for publication that might otherwise have gone to other researchers who consistently presented their work honestly.

The Panel wishes to emphasize that our decision concerns only the 11 charges of scientific misconduct specifically before us. It would be wrong to reach any conclusion based solely on our decision concerning other work produced by this active laboratory and its collaborators.

Below, we discuss the legal standards that governed our review and the background of the case before us. Next, we explain the record on which our conclusions were based. Then, we turn to our analysis of the specific charges against Dr. Angelides and, finally, our conclusions as to the appropriate remedies.

II. Applicable Legal Standards

The role of the RIAP is to provide an independent de novo review to researchers charged by ORI with scientific misconduct. See Acknowledgment of Request for Review at 3 (Apr. 21, 1997). The ORI Charge Letter and any supporting report, along with Respondent's appeal therefrom, frame the dispute and define the issues, but do not in themselves constitute any proof of misconduct. See Guidelines for Hearings before the RIAP at § III (rev. May 5, 1994) (Guidelines); John C. Hiserodt, M.D., Ph.D., DAB No. 1466, at 18-19 (1994) (Hiserodt). ORI has the burden of proving by a preponderance of the evidence adduced on the record before the Panel that scientific misconduct occurred as charged. 45 C.F.R. § 76.314(c)(1); 48 C.F.R. § 9.406-3(d)(3); Guidelines at § XI; Hiserodt at 19. This means evidence that is more convincing than the opposing evidence and shows as a whole that misconduct was more probable than not. Mikulas Popovic, M.D., Ph.D., DAB No. 1446, at 10 (1993) (Popovic). The Panel does not review ORI's procedures or the reasonableness of ORI's actions based on the evidence before ORI when it acted, but rather reaches its own conclusions based on the record developed by the parties in the proceedings before the Panel. See, e.g. Dr. Rameshwar K. Sharma, DAB No. 1431, at 10 (1993) (Sharma).

The Panel addresses two questions: whether scientific misconduct occurred as charged and, if so, whether the proposed actions are appropriate. In this case, ORI proposed two categories of actions. First, ORI proposed to impose administrative actions for a period of five years. The actions proposed consisted of prohibiting Dr. Angelides from serving in any advisory capacity to the Public Health Service (PHS), requiring any awardee institution for which Dr. Angelides performs research (subject to any debarment) to monitor for accuracy his PHS sponsored research, and requiring retraction of the challenged material in published papers. ORI Charge

Letter at 4-6.[1] The Panel's decision as to the proposed administrative actions constitutes the final agency action as to those matters. Guidelines at § X.

Secondly, ORI proposed to debar Dr. Angelides from receiving federal funds for a period of five years. Under the regulations governing such administrative debarments, these actions are discretionary actions to protect the integrity of federal funds. See 45 C.F.R. Part 76; 48 C.F.R. Subpart 9.4; and 48 C.F.R. Subpart 309.406. The usual time period for a debarment is three years, but a longer period is permissible where the facts warrant. 45 C.F.R. § 76.320(a)(1); 48 C.F.R. § 9.406-4(b). As to the debarment, the Panel makes findings of fact and conclusions of law by referral for the Debarring Official of the agency, who is the Deputy Assistant Secretary for Grants and Acquisition Management. Guidelines at § X. Regulations provide that the Debarring Official may reject the Panel's findings of fact, in whole or part, only after specifically determining them to be arbitrary and capricious or clearly erroneous. 45 C.F.R. § 76.314(b)(2); 48 C.F.R. § 9.406-3(d)(2)(ii); Guidelines at § X. The Debarring Official issues the final decision as to the debarment. Guidelines at § X. The findings of fact that we make below address both the issues of scientific misconduct and cause for debarment and administrative sanctions.

Department of Health and Human Services (DHHS) regulations (effective November 8, 1989) specifically define scientific misconduct as --

> 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.

45 Fed. Reg. 32,449 (Aug. 8, 1989), codified at 45 C.F.R. § 50.102. This definition directly applies to the Panel's evaluation of those alleged actions of Dr. Angelides occurring after its adoption. Dr. Angelides challenged the authority of DHHS to take action against him for those actions with which he is charged that allegedly occurred before November 8, 1989. (The charges relate to research reported in grant applications and publications between 1988 and 1992.) The RIAP has considered in prior cases whether DHHS had pre-existing authority and has uniformly concluded that the authority to act did not arise from the definitional regulation but rather from the DHHS's discretionary authority to protect the integrity of federal research grant funds. Sharma at 11. Indeed, the Departmental Appeals Board recommended debarments in scientific misconduct cases for conduct that occurred well before the adoption of the current definition. Robert Edward McCaa, Ph.D., DAB No. 823 (1987); Dr. C. David Bridges, DAB No. 1232 (1991).

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[1]Since the ORI Charge Letter refers to advising or using grant funds from the Public Health Service, we use that term for convenience for program components of PHS that have since been reorganized.

In regard to conduct alleged to have occurred prior to the adoption of the definition, ORI must demonstrate that the particular conduct charged would have violated standards of acceptable conduct among similarly-situated researchers at the time. Hiserodt at 16-18; Popovic at 10, n.4; Sharma at 11-12. However, prior rulings of the RIAP have established that, at a minimum, the "making of statements which are deliberately false or materially misleading about experimental results constitutes scientific misconduct," under prevailing standards in the scientific community even before the adoption of the explicit regulatory definition in 1989. See, e.g., Ruling in Sharma, DAB Docket No. A-93-50, at 12-13 (May 10, 1993); Hiserodt at 16-17 (1994).

Dr. Angelides argued that ORI failed to prove that the conduct alleged here so deviated from the standards of researchers at the time as to provide notice that such conduct would be regarded as scientific misconduct. Ang. Br. at 3. This argument is unpersuasive, however, in light of the fact that the conduct alleged, if proven, egregiously violated even the standards for conduct of a reasonable researcher articulated by Dr. Angelides himself. We consider in the body of the decision what the evidence proved as to the facts of Dr. Angelides's conduct. However, the conduct alleged was that Dr. Angelides intentionally presented data in grants and papers when he knew that the data were not what he claimed they were and that he intentionally claimed that research results had been obtained when he knew that the experiments either had never been done or had yielded no such results. Dr. Angelides's own testimony established that a principal investigator has a responsibility to verify personally data that he includes in publications or grants, and to consult with the experimentalist if any questions arise. Hearing Transcript (Tr.) at 1973-75 (Angelides); Ang. Br. at 135. Any intentional falsification of data and experimental results in grants and papers has always been regarded as misconduct in the scientific community, and with good reason, since it strikes at the heart of the scientific process which depends on honest reporting of results. On this point, the testimony of the scientific witnesses before us was uncontradicted. See, e.g., Tr. at 580, 658-59 (Pfenninger); Berget Written Direct Testimony (WD) at 8; Taylor WD at 7; Gilbert WD at 6; Patrick WD at 6. Thus, Dr. Angelides's collaborator, Dr. Joel A. Black, summarized the prevailing understanding, as follows: "It has always been absolutely unacceptable conduct within the scientific community for a scientist to intentionally present false data or to deliberately include materially misleading or inaccurate statements in a scientific paper or NIH grant application. I believe that a reasonable researcher in the field of neuroscience was aware of these standards within the scientific community in 1988 and 1989." Black WD at 5; see also Waxman WD at 5.

Further, the essential purpose of debarring researchers who commit scientific misconduct is to protect the federal government from committing scarce research grant funds to those who have already demonstrated a lack of integrity in their dealings. It is difficult to imagine conduct that would more directly impugn the integrity of a researcher in dealing with federal funding agencies than that alleged here -- lying about and falsifying data to substantiate incorrect claims about accomplishments achieved with federal funds to enhance one's own funding at the expense of honest applicants. The Panel thus rejected Dr. Angelides's claim that he lacked notice that the conduct with which he was charged would be regarded as scientific misconduct prior to November 1989. Whether Dr. Angelides engaged in the alleged conduct is a question of fact that

will be considered in the body of this decision, but the Panel concluded that, based on the law and the testimony in the record before it, such conduct, if proven, would constitute scientific misconduct even before the formal adoption of the DHHS definition.

Dr. Angelides also contended that he did not intentionally falsify the data involved or make intentionally false misrepresentations, but that, instead, he acted as a reasonable investigator interpreting data and relying on information obtained from subordinates. ORI's charges were limited to intentional fraudulent conduct. ORI did not argue that Dr. Angelides should be found to have committed scientific misconduct because his interpretation of data or his reliance on subordinates was not reasonable. Thus, the question before the Panel is not whether Dr. Angelides's alleged interpretations of data or reliance on subordinates was reasonable. We must either find that Dr. Angelides acted intentionally to falsify data and misrepresent research or we must find the charges unsubstantiated.

III. Prior History of the Case

The charges in this case arose from research that took place or was reported in grant applications and publications between 1987 and 1992.[2] During the period at issue, Dr. Angelides ran a laboratory at Baylor, first in the Department of Molecular Physiology and Biophysics and later in the Department of Cell Biology. The central focus of Dr. Angelides's research at issue here was the study of the voltage-gated sodium channel protein in nervous tissue. Sodium channels are membrane proteins that belong to a family of voltage-sensitive ion channels crucial to the ability of the nervous system to transmit an action potential. Dr. Angelides's laboratory employed a variety of methods to explore the structure, function, and distribution of sodium channels.

Data about which questions have been raised in this case originated with five different researchers who worked in Dr. Angelides's laboratory at various times: Mr. Mark Lewallen (in Dr. Angelides's laboratory at Baylor from 1986-1991), Dr. Barbara Wible (1986-1991), Dr. Lawrence Elmer (1986-1988), Dr. Owen Jones (1987-1991), and Dr. Jeffrey Wood (1987-1989).[3] In addition, Dr. Angelides alleged that some of the contested results came from the work of a sixth researcher, Dr. Thomas Nutter, who worked in Dr. Angelides's laboratory at the University of Florida but who did not accompany him to Baylor. The disputed claims arose from four major areas of research. The first concerned an effort to elucidate the location of disulfide bridges, molecular bonds within the sodium channel, that would provide information about the likely structure of the protein. The second involved the development of antibodies specific to segments of the intact sodium channel protein (anti-peptide antibodies). The third focused on a project to

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[2]The material facts set forth in this summary of prior events without citation are not in dispute.

[3]Several of these researchers had also spent time in Dr. Angelides's laboratory at the School of Medicine of the University of Florida in Gainesville before accompanying him to Baylor in 1986.

alter the protein by introducing fluorescently-labeled amino acids at identified sites in order to further explore the structure and functioning of the sodium channel. The fourth related to the characterization and use of a polyclonal antibody to the sodium channel.

In December 1992, allegations were raised by Dr. Arthur M. Brown, Dr. Angelides's former department chair, that Dr. Angelides had falsified data in grant applications submitted to NIH.[4] A Sub-Committee of three scientists at Baylor was formed to conduct an initial inquiry into these allegations. Dr. Angelides responded to the allegations by indicating that two of his former laboratory researchers, Dr. Wible and Mr. Lewallen, were responsible for the questioned data. The inquiry committee concluded that an investigation was warranted. A new Sub-Committee of seven Baylor scientists (Baylor Sub-Committee) was formed to conduct the investigation into the charges against all three respondents (Dr. Angelides, Dr. Wible, and Mr. Lewallen). The members were Drs. Susan M. Berget (Chair), Hiram F. Gilbert, Addison A. Taylor, Gretchen J. Darlington, Mary K. Estes, Peter D. Klein, and James R. Smith. During the investigation, the issues before the Baylor Sub-Committee were expanded, as a result of evidence or charges brought to the Sub-Committee's attention, to include alleged falsifications and misrepresentations in multiple grant applications and five published papers, grouped into nine issues. During the course of its investigation, the Baylor Sub-Committee took possession of data and notebooks stored in Dr. Angelides's laboratory and sequestered the materials as part of its review. The Baylor Sub-Committee concluded in its report issued on September 9, 1994 that a preponderance of the evidence established that Dr. Angelides was solely responsible for falsification, fabrication or misrepresentation in relation to five of the issues before it and that he committed these acts of scientific misconduct knowingly. Final Report Into Allegations of Misconduct in Science against Kimon J. Angelides, Ph.D, Baylor College of Medicine Sub-Committee on Scientific Integrity, at 5 (Sept. 9, 1994) (Baylor Report).[5]

Dr. Angelides sought further review of the charges by an Appellate Committee at Baylor, consisting of five different Baylor scientists. After concluding its review, the Appellate Committee unanimously upheld the conclusions of the Baylor Report.

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[4]The inquiry which resulted in the present charges was the second time that allegations of misconduct were made by Dr. Brown against Dr. Angelides. The first inquiry initiated in July 1992 addressed a different set of allegations and did not result in an investigation.

[5]On August 1, 1994, Dr. Angelides filed a response to a draft version of the Baylor Report, in which he disputed the basis for the Baylor Sub-Committee's findings and conclusions. Baylor Report at 503 (Ang. Resp. to Draft Baylor Report). The final Baylor Report included a rejoinder from the Sub-Committee to Dr. Angelides's arguments, a further response from Dr. Angelides dated August 26, 1994, and an additional response from the Sub-Committee. Baylor Report at 503, 531 and 537. In addition, Dr. Angelides filed a further response to the final report. Ang. Resp. to Baylor Report (Sept. 19, 1994).

On March 10, 1997, ORI issued 11 formal charges of scientific misconduct against Dr. Angelides, along with numbered factual findings and analyses derived from ORI's oversight investigation and review of the Baylor Sub-Committee proceedings and Report. ORI Findings at 4.[6] On April 8, 1997, Dr. Angelides filed his appeal from these charges with the RIAP. The proceeding was stayed for several months at the request of Dr. Angelides because of the pendency of other proceedings. An in-person hearing was held before the full Panel for two weeks in Houston, Texas, in March-April 1998; post-hearing briefing ensued, and the record closed on December 15, 1998.

IV. The Record before this Panel

Since the Panel's review is de novo, our deliberations in this case were based entirely on the record before us. This section describes the record that the parties presented to the Panel, including documentary evidence and witness testimony, and addresses several challenges to the integrity of that record.

The record in this case consisted of the submissions and arguments of the parties, and the evidence in the form of exhibits[7] and the testimony of witnesses received both in written form and orally at the hearing. A total of 24 volumes of exhibits was accepted into the record, supplemented by additional materials received into evidence at and after the hearing. As noted, the ORI charge letter and Baylor Report, along with Dr. Angelides's appeal and the attachments thereto, are in the record and frame the scope of the issues before us, but do not constitute affirmative evidence of the propositions set forth in them.

From his first submission to this Panel, Dr. Angelides's appeal has focused on attacking the process of the Baylor investigation as biased and unfair to him. See, e.g., Ang. Appeal of Charge Letter at 3-5. In ruling on this issue, the Panel noted that its de novo review process provides an independent and impartial adjudication of the facts and merits of the charges against Dr. Angelides, rather than an evaluation of prior proceedings. Ruling on Preliminary Legal Issues (Legal Ruling) at 2 (December 30, 1997); see also Thereza Imanishi-Kari, Ph.D., DAB No. 1582, at 3 (1992). To the extent that Dr. Angelides's complaints went to the adequacy or fairness of

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[6]Dr. Angelides argued that ORI advanced additional charges during these proceedings. Ang. Br. at 2. The Panel did not consider any charges not set forth in ORI's charging papers, and the Guidelines provide that the dispute is framed by the initial charges and report and the appeal filed to them. Guidelines at § III. Therefore, it is not necessary to address this argument further.

[7]An initial set of exhibits submitted jointly are denominated Record Exhibits. Each party submitted a set of exhibits, denominated ORI and Angelides Exhibits. Further exhibits were received at the hearing, called Hearing Exhibits. Many of the hearing exhibits were originals of materials that appeared in photocopy form in the record or party exhibits. A number of other original materials that were received into evidence after the hearing were denominated Panel Exhibits.

the procedural and administrative process provided by Baylor or ORI, these complaints, whatever their merit, are not relevant here because he has had an opportunity to present all the relevant evidence and confront all the relevant witnesses in the full and fair hearing process guaranteed before the Panel. Legal Ruling at 2. The Panel instructed Dr. Angelides that he could nevertheless raise arguments that prior events had impacted the record before the Panel either by affecting the availability or authenticity of particular documentary evidence or by influencing the availability or content of any witness's testimony. Id. at 3-4. However, the Panel stressed that, to be persuasive, any such arguments had to be founded not merely on general or unsupported allegations, but on a factual showing as to their basis, such as specifying what evidence would have been available, why and how it came to be missing, and what probative value Dr. Angelides contends that it would have had. Id.

After careful review of all the evidence presented to it, the Panel concluded that Dr. Angelides failed to present any persuasive evidence that the record before this Panel was materially compromised by the actions of the Baylor Sub-Committee or ORI. Dr. Angelides's allegations in this regard fell into two main areas: allegations of destruction or loss of documentary evidence and allegations of witness intimidation. The Panel took each allegation of this nature seriously and carefully considered the merits of each to ensure that the record before it was not tainted.

The procedures established by the Panel provided assurances to the parties that the Panel would enforce access to the records retained by Baylor and permitted full discovery, yet at no time did Dr. Angelides seek any discovery order from this Panel regarding records in Baylor's sequestered files despite repeated opportunities to do so. See, e.g., Reminder of Briefing Schedule at 2 (Aug. 1, 1997); Legal Ruling at 6-7 (Dec. 30, 1997). The Panel ruled that, in order to sustain its case, ORI had to provide full access to all relevant data and other original materials both to Dr. Angelides and to the Panel itself. Summary of Telephone Conference at 2 (May 19, 1997); Ruling on Ang. Objections to ORI Exhibits at 2 (March 10, 1998). The Panel further instructed ORI to require Baylor to cooperate in providing such access. Summary of Telephone Conference at 2 (May 19, 1997). In addition, the Panel ordered ORI to have Baylor produce at the hearing site in Houston all relevant sequestered records. Id. at 2-3. Dr. Angelides had full access throughout the hearing period to all the contents of Baylor's records under the supervision and control of Panel staff. In light of this process, it was incumbent on Dr. Angelides to bring to the attention of the Panel in a timely manner and with specificity any concerns he had about the contents of the files maintained by Baylor. At no time during the pre-hearing period or at the hearing itself did Dr. Angelides raise any question about specific documents that he believed should have been in those files but were not. Had such a question been raised immediately, the Panel would have been in a position to verify whether the allegedly missing item was or was not in the files and would have been able to immediately call and question witnesses responsible for the contents and custody of Baylor's sequestered files.

Instead, Dr. Angelides waited until his reply brief and subsequent motions to raise allegations that relevant data had disappeared from the record either as of or after the hearing and to ask the Panel to draw an inference that documents must once have existed that supported Dr.

Angelides's case and that ORI or Baylor were responsible for their loss. Ang. R. Br. at App. 2. ORI responded that the motion was untimely. ORI Resp. to Ang. Claim of Spoliation at 2-5. Furthermore, ORI argued that Dr. Angelides failed to lay any foundation on which to conclude that additional relevant data ever existed. Id. at 6-7. The Panel concluded that ORI's position was correct.

Dr. Angelides argued that his motion was not late, even though it came long after the close of the period set for discovery, submission of exhibits and receipt of testimony, indeed long after the end of the hearing and near the close of the briefing period. Ang. Reply to ORI's Resp. to Spoilation Motion at 1. He argued that ORI failed to provide him with notice that the case against him rested on an adverse inference from the absence of data because ORI asserted in its preliminary legal brief that its case was "not about missing data." Id.; ORI Opposition to Ang. Prelim. Br. of Legal Issues at 8 (ORI Prelim. Legal Br.) (emphasis in original). Dr. Angelides's argument is wrong on two points.

First, the case against him does not depend on drawing a negative inference from the absence of data.[8] Many issues in the case (the substance of which is discussed in detail in later sections), depend on evidence that extant data were falsely described in figures presented in published

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[8]Dr. Angelides also argued that he could not be held responsible for the absence of supporting data because applicable federal regulations required only that records be retained for three years. Ang. Appeal Letter, Tab B at 2. Regulations governing those who receive DHHS grant awards require all records pertinent to an award to be retained "for a period of three years from the date of the submission of the final expenditure report." 45 C.F.R. § 74.53(b). When any claim or litigation arises before the expiration of that three-year period, "the records shall be retained until all litigation, claims, or audit findings involving the records have been resolved and final action taken." Id. at § 74.53(b)(1). This provision does not relieve Dr. Angelides of responsibility as a matter of either law or fact. Dr. Angelides failed to establish the start of the record retention period for any of the contested data, by demonstrating when the final reports of his research relating to any of the contested data were submitted. However, at a minimum, once the charges were filed against Dr. Angelides, he was on notice that he should retain all data and records involving those charges. The earliest experimental work at issue was allegedly performed in 1987 and 1988 (mostly antibody production). Presumably, the final reports for work in those years were not submitted until some time after the close of the grant years. Once the charges were filed against Dr. Angelides, which occurred in December 1992, he was obligated to retain all extant records. As a matter of law, there was at best a small window of time during which the records could have been legally discarded. However, Dr. Angelides offered no testimony himself or from others to suggest that he, in fact, disposed of such records during that period. To the contrary, he agreed that he retained possession of the data of researchers who worked in his laboratory when they departed. The record shows that other data of the experimentalists involved were available from the same time frames, and Dr. Angelides offered no plausible explanation as to why he would have retained those data but discarded the data the existence of which was at issue here.

papers and grant applications. Even in those areas where the charges are that statements were made in grant applications about experimental results that did not exist (such as the challenged anti-peptide antibodies and the disulfide bridges), the charges were founded primarily on testimony from the actual experimentalists that the research in question was either never done at all or never yielded the claimed results, corroborated by other witnesses' testimony as well as the absence of any data contradicting that testimony. Furthermore, in many instances, the research records of the experimentalists involved contain evidence of repeated unsuccessful efforts, so that the record is not merely one of missing data but of affirmative evidence of lack of success.

Second, it is disingenuous for Dr. Angelides to argue surprise about ORI's position that his failure to produce any data to support the claims made in his grants was further evidence that the claims were unfounded. Dr. Angelides argued in briefing preliminary legal issues in this case that the absence of primary data had been used to support findings against him. Ang. Prelim. Legal Br. at 21. Dr. Angelides was thus well aware that the absence of supporting data was relevant to the case against him. ORI's findings supporting the charges (as well as the Baylor Report which ORI adopted) provided adequate notice to Dr. Angelides that the absence of data supporting his claims was a relevant factor.[9]

Even had the spoliation motion not been submitted so late in the process as to raise a question as to the good faith of the proponent, it was without merit. Dr. Angelides enumerated in an appendix to his reply brief seven items which he alleged had been unavailable to him due to the actions of Baylor or ORI. Ang. R. Br. at App. 2. Of these seven items, only a few actually related to documents that were purportedly lost or destroyed. The first item was a logbook of Baylor's oligonucleotide facility which was not among the sequestered materials in Baylor's possession. The logbook was subsequently obtained by ORI from the scientist who had run the oligonucleotide facility during the relevant time period and who had retained the logbook, and the original was submitted for the record on the order of the Panel. See Ruling on Outstanding Motions, at 4 (October 26, 1998); ORI Resp. to Ang. Claim of Spoilation at 6, n.4 and Atts. 2 and 3. The sixth item did not involve any specific materials but rather argument that went to claims of the Baylor Sub-Committee's "general lack of organization and loss of evidence." The seventh item was materials of Dr. Wood's which were in fact in the Panel's record. Hearing Ex. 8.

Turning to the remaining items which involved specific materials not included in the Panel's record, the Panel concluded that Dr. Angelides did not make a persuasive case that any of the items were lost or destroyed or withheld from him in bad faith. Item two, as further clarified by

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[9]For example, ORI found that Dr. Angelides had acknowledged before the Baylor Sub-Committee that Mr. Lewallen's notebooks contained "no evidence to support the conclusion . . . that his laboratory had identified any specific disulfide bridges in the sodium channel." ORI Findings at ¶10. Also, ORI found that, although Mr. Lewallen "maintained detailed records of peptides that he synthesized," Baylor had concluded that "there was no evidence that Mr. Lewallen made peptides that were not documented." ORI Findings at ¶521.

Dr. Angelides's counsel during a telephone conference, related to a claim by Dr. Angelides that he was aware of a set of computer disks that contained additional data of Mr. Lewallen's which he wished to print out to determine if they might contain helpful information. Since Dr. Angelides offered no explanation for his failure to seek this material during discovery or at the hearing, and even his counsel acknowledged that they were aware of its existence since at least September 1997, the Panel concluded that the belated (and speculative) request should be denied. Ruling on Outstanding Motions at 4-5. Item three was a claim that Mr. Lewallen at one time had immunoblot and immunoprecipitation data relating to those anti-peptide antibodies that ORI charged were never made as claimed in the grant applications. The evidence before the Panel (discussed in more detail in the section on the anti-peptide antibodies) corroborated Mr. Lewallen's testimony that these data never existed, and, therefore, were not lost or destroyed. Item four was a claim that certain experiments which Dr. Angelides asserted he performed himself were documented in a manila folder that was not found in Baylor's sequestered records. As discussed in more detail in the section on the florescent amino acid project, Dr. Angelides's own testimony about these purported notes was inconsistent and he presented no testimony other than his own claims to substantiate the existence of such a manila folder. For example, no other laboratory member testified to Dr. Angelides having performed the experiments or to having ever seen this folder or its contents. Finally, item five was a claim that negatives had been removed from two envelopes contained within Dr. Elmer's records. Cf. Hearing Exs. 14 and 15. The contents of these two hearing exhibits were exhaustively detailed by descriptions read into the record in the presence of both parties. Tr. at 967-72. Neither Dr. Angelides nor his counsel objected that items were missing from those records. Dr. Elmer expressly denied that he ever obtained the data (which, as discussed in more detail below, Dr. Angelides now alleges were for a purported 18-lane composite figure on the tissue specificity characterization of the polyclonal antibody) that Dr. Angelides asserted would have been recorded on these negatives. Elmer WD at 40-41. The Panel concluded as to this item as well that there was no evidence that the data ever existed and, therefore, no evidence that ORI or Baylor had lost or destroyed them.

Further, the evidence adduced at the hearing contradicts Dr. Angelides's spoliation charges. Dr. Gilbert testified without contradiction that:

> The Sub-Committee initially requested that Dr. Angelides turn over to the Sub-Committee all documents relevant to the allegations. As new allegations were raised, we requested any additional relevant documents. All documents received by the Sub-Committee were secured in the Offices of Research or Vice-President for Legal Affairs. The records were stored in a secure room. The Office of Research or Office for Legal Affairs was responsible for maintaining these records and supervising access to these documents. . . . As far as I know, there were no specific research records that were lost or destroyed by the Sub-Committee.

Gilbert WD at 8-9; see also ORI Letter to Panel, dated August 19, 1998, at Att. A (Affidavit of Sharon K. Edmonds, Baylor Record Custodian). Dr. Angelides had the opportunity to cross-examine Dr. Gilbert and two other members of the Baylor Sub-Committee who were called as

witnesses by ORI and yet asked no questions of any of them about the handling of sequestered materials or the contents of the Baylor files. Dr. Angelides called no witnesses himself to testify to how the documents were sequestered, what was taken, and what was contained in the files at any point when they were accessed and reviewed. Dr. Angelides asserted that he would call as a witness Dr. Jeffrey Rosen, who was his faculty advisor during the Baylor investigation and who, he said, would be able to substantiate his allegations concerning the improprieties in the Baylor proceedings. Ang. Witness List at 2. Thus, Dr. Angelides claimed that Dr. Rosen "observed first hand the numerous instances in which witnesses were subject to intimidation [and] duress" and "was present to observe the lack of document control as the underlying investigation seized primary data which later turned out to be lost or destroyed," and, indeed, had himself "withstood numerous attempts at intimidation." Id. Dr. Rosen did not testify to any sign of data tampering or witness intimidation by the Baylor Sub-Committee. In fact, he reported that his impression was that the Sub-Committee was "trying to do the best job they could at the time. . . ." Tr. at 1203 (Rosen). Dr. Angelides did not present any other witness who supported these allegations.

In any case, as explained in more detail in the discussion of the issues below, Dr. Angelides has been unable to point to any missing data that, if located, could conceivably alter the conclusions that he falsely presented well-labeled primary data or claimed accomplishments that he could not have believed were achieved in his laboratory in the face of the cumulative testimony to the contrary. For example, even were Dr. Angelides able to produce immunoblots demonstrating that the polyclonal antibody had performed as claimed as to molecular weight or tissue sources, that would not alter the conclusion that the data which Dr. Angelides in fact presented to support those claims were fabricated. Furthermore, Dr. Angelides provided no credible evidence that much of the material to which he referred as missing ever existed. For example, in regard to Dr. Angelides's assertion that Mr. Lewallen had accumulated large amounts of data that collectively supported claims made in the grant applications but that were no longer available or in existence, this assertion contradicted both Dr. Angelides's own position before the Baylor Sub-Committee that he himself could find nothing in Mr. Lewallen's records or notebooks to support the claims (which he said Mr. Lewallen made to him) and Mr. Lewallen's testimony that such data never existed. As discussed below, the Panel concluded that Mr. Lewallen's testimony was credible and corroborated in many respects by other laboratory members who were aware of his failures and frustrations and by Mr. Lewallen's thesis committee.

The conclusion that the record before us has not been tainted does not mean that the conduct of the investigation at Baylor was irreproachable. It was undisputed that the Baylor Sub-Committee made no contemporary inventory of the documents of which it took possession. Clearly, a signed and dated inventory of each document received and sequestered would have been a preferable practice and would probably have obviated the need for this after-the-fact review of claims of missing materials. Nevertheless, Dr. Angelides pointed to no explicit requirement that institutional review bodies create inventories of records as received. Furthermore, as explained above, Dr. Angelides did not make any persuasive showing that any such deficiency in the chain of custody resulted in prejudice to him. In addition, the Baylor Sub-Committee took possession of a number of records from the Baylor Medical Illustrations facility (Medical Illustrations)

relating to photographing, printing, copying and construction of figures from data at issue in this case. Unfortunately, in making additional prints and composites for its own use, the Baylor Sub-Committee did not always preserve a clear paper trail to distinguish which prints resulted from later orders. Further, ORI failed to place many of the original Medical Illustration files in the record, even though the available copies were sometimes contested or illegible. Where this has compromised our ability to determine who sought a particular print or who requested a particular construction, we have not relied on this evidence.

We turn next to Dr. Angelides's allegations of witness tampering. In his brief on preliminary legal issues, Dr. Angelides alleged that "numerous witnesses were subjected to harassment, intimidation and deprivation of materials essential to the matters under review." Ang. Prelim. Legal Br. at 18. The two examples on which Dr. Angelides relied in his preliminary brief were allegations concerning the treatment of Ms. Wanda Quezada (a former secretary who did some of the typing on grant applications) and Dr. Lawrence Elmer (a former graduate student of Dr. Angelides's) by the Baylor Sub-Committee. The Panel concluded that, even treating the evidence offered by Dr. Angelides about these two witnesses in the light most favorable to him, no support could be found for any claim of intimidation or witness tampering. Legal Ruling at 4-5 (Dec. 30, 1997). However, the Panel preserved Dr. Angelides's opportunity to present evidence at the hearing of intimidation or other improper influence on witness testimony. Each of these witnesses testified in person at the hearing in this case. Their testimony offered no suggestion of improper influence nor did any other witness offer testimony supportive of these claims.

Dr. Angelides further charged that the written direct testimony of witnesses who appeared against him was scripted or rehearsed because each witness reviewed and edited several versions of the testimony, which had been initially drafted by counsel after interviews with the witnesses, before signing and submitting it. Ang. Br. at 3-5. In the case of witnesses represented by counsel (including counsel for Baylor for those employed by Baylor), witnesses' counsel, as well as counsel for ORI, participated in the process. Dr. Angelides described this process of preparing written direct testimony as "appalling and overt . . . witness interference" by ORI and Baylor counsel, and contrasted it to his procedure of submitting questions and answers without revisions. Ang. Br. at 3-4. The Panel did not dictate any particular manner of preparation and found no impropriety in the procedure adopted by ORI. See Panel Ruling on Ang. Objection to ORI Written Direct Testimony at 3 (March 13, 1998). Every witness was required to sign a statement as part of the written direct testimony indicating that they knew that any untruthful testimony they offered could have result in prosecution.. Id. at 2-3. Every written direct submitted by ORI did contain the required statement, acknowledging responsibility for the truthfulness of the testimony. Berget WD at 1; Benke WD at 1; Black WD at 1; Elmer WD at 1; Gaskell WD at 1; Gilbert WD at 1; Hamilton WD at 1; Jones WD at 1; Jones WD at 1; Lewallen WD at 1; Nutter WD at 1; Patrick WD at 1; Taylor WD at 1; Velazquez WD at 1; Waxman WD at 1; Wible WD at 1; Wood WD at 1. Every witness against him whom Dr. Angelides chose to call for in-person cross-examination affirmed that the written direct testimony as submitted represented their own truthful testimony. Tr. at 11 (Berget), 247-48 (Hamilton), 276 (Wible),

324-25 (Gaskell), 350 (Nutter), 379 (Velazquez), 486 (Jones), 668-69 (Taylor), 730 (Gilbert), 792 (Wood), 887 (Elmer), 1026 (Patrick)(with editorial changes made on record), 1054 (Benke), 1104-05 (Lewallen)(with editorial changes made on record). Not a single witness suggested that their testimony had been influenced improperly in any way or that they had felt pressured or dictated to. It was plain to the Panel, as it observed the demeanor of these witnesses, that the scientists who were testifying felt free to express their own thinking and that they were not overawed by the lawyers or legal proceedings. Given that a large number of the witnesses (both fact and expert witnesses) had already been named as defendants in Dr. Angelides's civil suit, it is understandable that they would include their own counsel or that of Baylor in the process of preparing for their testimony, but there was no basis for the allegations of witness tampering or coercion in regard to the written direct testimonies offered on behalf of ORI.

Dr. Angelides also attacked as biased the testimony of those witnesses who appeared against him as experts who had previously served on the Baylor Sub-Committee or the Baylor Appellate Committee, and who, consequently, "entered the ORI oversight review and this appeal with a preconceived and established position that was adverse to Dr. Angelides." Ang. Br. at 8. The Panel concluded after hearing these witnesses that there was no evidence that they entered their initial participation in the Baylor proceeding with any pre-existing bias against Dr. Angelides.[10] It is unquestionably the case that, by the time they appeared on behalf of ORI, Drs. Berget, Gilbert, Taylor, and Patrick had previously formed opinions about Dr. Angelides's conduct as a result of their participation in the Baylor proceedings. Clearly, the Baylor Report, in addition to the written direct testimony of these witnesses, gave Dr. Angelides detailed notice of the nature and bases of these opinions, so he was enabled to prepare thoroughly for cross-examination. It was also true that Dr. Angelides named several of these individuals as defendants in his civil suit, which might impact their interests, raising the danger of a conflict of interest. Id. However, in no instance did the Panel find that the opinions of any of these scientists changed substantively from those expressed in the Baylor Report (issued before the civil suit), so the Panel concluded that it was unlikely that the testimony of these witnesses was impacted by self-interest.

Dr. Angelides did not establish that it was improper for ORI to present the members of the Baylor review committees to explain the detailed basis of the conclusions reached in the Baylor Report. Nevertheless, it might have been preferable for ORI to have presented additional or different individuals as expert witnesses who did not have prior involvement in the case, in order to provide a further, fresh assessment of the evidence as it was presented to this Panel. The Panel concluded that its decision-making was, in any event, not compromised by the choice of experts, because, in the vast majority of the issues, the expert testimony of these witnesses was either uncontested, corroborated by other independent scientists who appeared before the Panel, or peripheral to the factual evidence that established misconduct.

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[10]In the case of Dr. Patrick, Dr. Angelides had himself recommended Dr. Patrick to be a member of the Appellate committee reviewing his case on the basis that Dr. Patrick had no potential bias and had "demonstrated and respected expertise in each and every aspect of the scientific issues under discussion." Hearing Ex. 35.

Dr. Angelides presented two expert witnesses in support of his case: Dr. Lee Limbird and Dr. Karl Pfenninger. The Panel found both of these witnesses credible and well-qualified. However, the testimony which Dr. Angelides presented from these witnesses was narrow and did not contradict ORI's witnesses on essential factual matters. The testimony of Dr. Angelides's witnesses went largely to the claims made in figures in one paper relating to the characterization of a polyclonal antibody to the intact sodium channel, which is discussed in detail in the last section of the analysis portion of this decision. They offered no opinion on whether Dr. Angelides committed scientific misconduct with regard to most of the other issues addressed in this decision. Tr. at 567-70, 575-76 (Pfenninger); Tr. at 1807-08 (Limbird). Further, they testified that they were provided a limited set of information to review in forming their opinion. Thus, they did not review the ORI charges against Dr. Angelides; they were not provided with the written testimony of ORI to review; they had never talked to any of the experimentalists. Tr. at 567 (Pfenninger); Tr. at 1805-06, 1809 (Limbird). Ultimately, the standard for scientific conduct which these witnesses articulated for Dr. Angelides was consistent with that presented by other scientists. Thus, Dr. Limbird testified that "accuracy is essential, inadvertent error is human." Limbird WD at 4. Dr. Pfenninger agreed that knowing misrepresentation of data in a grant or paper at all times constituted scientific misconduct, and that "[s]cientific misconduct refers to honest data presentation." Pfenninger WD at 7 (emphasis added); see also Tr. at 640.

Many of the other witnesses who testified for Dr. Angelides were scientists who stated that they did not encounter any evidence during their collaborations with Dr. Angelides or during their time in his laboratory that led them to question his integrity. See, e.g., Maleic-Jericevic WD passim; Benos WD passim; Block WD passim; Devor WD passim; Kempner WD passim; Epstein WD passim. The Panel found this testimony generally credible but not helpful to its deliberations, to the extent that these witnesses were not aware of the facts that formed the basis of the charges in this matter.

Finally, Dr. Angelides charged generally that ORI had an improper "unity of purpose" with Baylor, which had interests adverse to Dr. Angelides in light of the pending civil litigation. Ang. Br. at 16. Federal regulations contemplate a division of responsibilities in addressing charges of scientific misconduct between institutions receiving federal research funds and ORI. See generally 42 C.F.R. Part 50. Grantee institutions are obligated to cooperate in the investigation of charges of scientific misconduct. 42 C.F.R. § 50.103(c)(4). It was hence entirely appropriate that Baylor, having found that scientific misconduct occurred, would report its findings to ORI and cooperate with ORI's further proceedings. Further, ORI had, of necessity, to work with the grantee institution that conducted the original investigation in order to determine whether the final report was well-founded and to decide whether additional clarification or investigation was required. See 42 C.F.R. § 50.104(a)(6). The filing of a lawsuit against Baylor by Dr. Angelides did not change the essential relationship between ORI and the grantee institution or render their discharge of their overlapping responsibilities somehow sinister. To accede to Dr. Angelides's position on this issue would effectively place in the hands of every respondent facing scientific misconduct charges the ability to paralyze the federal government by the simple expedient of filing a civil suit against the institution that conducted the investigation.

We turn next to our findings and conclusions as to each of the charges against Dr. Angelides. We have grouped the charges for discussion by the four major research projects in relation with which Dr. Angelides is charged with falsification or misrepresentation. We consider first the charges relating to the disulfide bridges project, followed by the charges relating to anti-peptide antibodies, the florescent amino acid project and the anti-sodium channel antibodies project, in that order.

ANALYSIS

I. Disulfide Bridges Project

A. Introduction on the disulfide bridges

One of the goals for which Dr. Angelides sought funding in grant applications to the NIH was an effort to locate disulfide bridges in the sodium channel protein. Disulfide bridges can form in a protein molecule when sulphur groups in cysteine amino acids interact; the formation of disulfide bridges is one constraint on the way that the protein molecule folds into a characteristic structure. See Taylor WD at 9; Lewallen WD at 3.

In grant applications submitted between April 27, 1988 and January 31, 1992, Dr. Angelides made a series of statements asserting that his laboratory had succeeded in locating a number of disulfide bridges and, in two of the grants, identifying specific locations of disulfide bridges. Mr. Lewallen was the researcher assigned to this project. The applications contained descriptions of the methods used, including using either the enzyme trypsin or the chemical cyanogen bromide (CNBr) to cleave the protein into peptide fragments for further analyses. In two of the same grant applications, Dr. Angelides also presented data in two figures in the appendices in the form of mass spectrometry and high pressure liquid chromatography (HPLC) results that purport to show analyses of peptide fragments of the sodium channel as part of the process by which the bridges were identified. ORI charged that these claims by Dr. Angelides in each of the grant applications were intentionally falsified and the supporting data were not what they purported to be. Before Baylor, Dr. Angelides formally accused Mr. Lewallen of scientific misconduct, in part based on questions about the data at issue in this section. See ORI Ex. 30, at 5. Before the Panel, Dr. Angelides took the position that it had not been proven that disulfide bridges could not have been identified and denied he knew the data in the grant were not accurately presented. Ang. Br. at 20, 33, 39.

In this section, we discuss first the textual claims in grant applications about the disulfide bridges project and then the presentation of HPLC and mass spectrometry data in figures in two grant applications.

B. Textual claims about disulfide bridges

The earliest grant application in connection with which Dr. Angelides is charged with making false claims concerning the disulfide bridges project is NS01218-02, one in a series of continuing applications for career support awards, submitted on April 27, 1988, which stated that: "Combined protein chemical and sequence information has revealed three of the channels disulfide bridges." Record Ex. 2, at 8 (original grant application at Panel Ex. 7). The grant application describes the methods used to identify the bridges by enzymatic cleavage to create small peptide fragments, which were then separated by HPLC, and analyzed for cysteic acid, whereupon the "disulfide bond containing peptides are identified." Id. The same claim of having identified three bridges recurs in NS01218-03, submitted on April 25, 1989, with an additional description of a "complementary approach toward elucidating the disulfide bridges" used in the intervening year. Record Ex. 3, at 7 (original grant application at Panel Ex. 8). The new approach involved using a cDNA clone to produce sodium channel protein with a radioactive tracer (^{35}S-Cys) identifying peptides linked by disulfide bridges. Id. These peptides were then microsequenced. Id. Virtually identical claims were made in successive renewal applications in 1990 and 1991, except that the text refers to "several" disulfide bridges having been revealed, rather than "three." Record Ex. 4 (NS01218-04, submitted April 19, 1990), at 7-8 (original grant application at Panel Ex. 9); Record Ex. 5 (NS01218-05, submitted April 17, 1991), at 7 (original grant application at Panel Ex. 10). The last application also states that, alternatively, mass spectrometry has been applied for the entire digest. Record Ex. 5, at 7.

In two other grant applications, submitted for competitive funding in 1989 and 1992, Dr. Angelides provided more specific information about the precise purported locations of disulfide bridges and more details about the methods used to identify them. In NS24606-05, submitted on June 28, 1989, Dr. Angelides stated that:

> With the primary sequence of the NaCh known we sought additional information that would place model-independent constraints on its folding. To determine the location of the disulfide bridges, purified NaChs were exhaustively labeled with N-ethlymaleimide under denaturing conditions, digested with trypsin, chymotrypsin, V8 protease (or pepsin), and the peptides separated by HPLC (Figure 1-Appendix). Each peak was isolated and analyzed for cysteic acid, which is a by-product of cystine. Cysteic acid containing peptides were rechromatographed and sequenced. We have found that Cys^{337} and Cys^{346}, are linked in an extra-cellular loop (which is 100% conserved in all NaChs) between putative transmembrane S5 and S6 and Cys^{902} and Cys^{1119}, which are between the C-terminal side of S7 segment in domain II as it emerges from the membrane, and a cytoplasmic loop are linked. The latter disulfide is unusual because of the number of intervening amino acids (38, 39). Chemical modification indicates that of the 38 cysteines, 12 of these are involved in disulfide bridges.
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> Because this method requires large amounts of protein and is time-consuming (i.e. each HPLC peak needs to be amino acid analyzed), we have added *in vitro* translated NaCh with [^{35}S]-Cys as a tracer, to help identify disulfides. Only [^{35}S]-

> Cys containing and not [^{3}H]-NEM/[^{35}S]-Cys peptides are analyzed thus reducing the number of amino acid analyses.

Record Ex. 9, at 22-23 (emphasis added) (original grant application at Panel Ex. 4). In GM48816-01, submitted on January 31, 1992, Dr. Angelides repeated much of the information above in different language, including the claims of specific disulfide bridge locations, but with some substantive changes to the description of methodologies. Record Ex. 13, at 14. In addition to the enzymes listed for use in digesting sodium channel, the GM48816-01 grant states that digestion was done "in some cases by CNBr alone." Id. Again referring to the laboriousness of the method described, this grant states that a "more sensitive detection and chemical characterization method" has been developed to identify disulfide-linked peptides using CNBr cleavage, HPLC separation, and analysis by hybrid tandem mass spectrometry. Id.

ORI charged that these claims were false in that research results did not establish that any disulfide bridges in the sodium channel had been identified (including those specifically claimed between Cys^{337} and Cys^{346} and between Cys^{902} and Cys^{1119}), that 12 out of 38 cysteines in the sodium channel were involved in disulfide bridges, or that [^{35}S]-Cys-labeled in vitro translated sodium channel protein had been used as a tracer in identifying disulfide bridges. ORI charged that Dr. Angelides intentionally falsified these claims. ORI Findings # 1-A, at 10.

Before the Panel, Dr. Angelides argued that the claims made in the grant applications were based upon his "reasonable judgment of the data that Mr. Lewallen presented to him." Ang. Br. at 20. In earlier correspondence with the Baylor Sub-Committee and in his testimony before Baylor, however, Dr. Angelides denied that any documentation existed in Mr. Lewallen's records to support the claims and asserted that he had concluded that all data supplied by Mr. Lewallen were "suspect." See Record Ex. 21, at 60-66, 76; Record Ex. 32, at 1. The Panel therefore considered whether the claims made were supported by data or other evidence which could reasonably be interpreted as claimed, whether Dr. Angelides was responsible for the inclusion of these claims, and whether (assuming the claims were unsupported and that Dr. Angelides was responsible for their inclusion) the claims were the result of good faith reliance on Mr. Lewallen or of intentional misrepresentation by Dr. Angelides of the status of this project.

1. Primary data relating to identification of disulfide bridges

Dr. Angelides proffered no primary data to document that his laboratory had identified the location of any disulfide bridges in the sodium channel, and the Panel has not located any such data in the record presented to it.

The experimentalist on the disulfide bridges project was Mr. Mark Lewallen, a graduate student, who worked with Dr. Angelides from 1985 (beginning in Florida) until 1991 when he left Dr. Angelides's laboratory after his candidacy for a doctorate ended with a terminal Master's degree. Lewallen WD at 2. Mr. Lewallen testified that he had not succeeded in locating any disulfide bridges, and that he had never led Dr. Angelides to believe that he had. Id. at 7-8, 15, 25-26. He

further testified that he never obtained reproducible HPLC results, despite repeated attempts,[11] and that he was unable to get useable mass spectrometry results from sodium channel peptides submitted to the mass spectrometry facility. Id. at 5-7. He denied that he ever received any meaningful results from any submission to the facility. Id. at 6; Tr. at 2092 (Lewallen).

Dr. Angelides himself stated that the identification of disulfide bridges as reported in the grant applications would require "HPLC profiles, amino acid analyses of cysteine byproducts (cysteic acid), peptide sequencing, and/or mass spec profiles, all properly cross-referenced to each other." Ang. Br. at 23, n. 20. Hence, a substantial paper trail would have been generated in the process. Dr. Angelides argued that no "analysis was presented [by ORI] on the data missing in the records that proved the preliminary progress reported in the grant applications could not or had not been made, nor any scenario to reconstruct how the data contained within the experimental records could not have been used to identify disulfide bridges." Ang. Br. at 20. From this assertion it was not clear to the Panel if Dr. Angelides was implying that relevant data used to arrive at the challenged claims had never existed or had been lost.[12]

Before Baylor, as noted, Dr. Angelides had indeed asserted that he "could not find any evidence in Mr. Lewallen's notebooks on the determination of the number of disulfides." Ang. Resp. to Baylor Report at 202. He testified before Baylor that he would not have known it "had this investigation not started," but that "in hindsight" he realized that there was "no data that would support that conclusion" and that he had "made that assessment" himself. Id. at 201. His

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[11]Mr. Lewallen described the efforts he made to obtain such results, as follows: "I tried to fragment the denatured protein with the enzyme trypsin, that cuts at defined sites in the protein chain. I would then attempt to separate these fragments by HPLC. . . . I would try to recover the peaks eluted from the column. I then attempted to analyze the material by a number of different methods, i.e., mass spectrometry, cysteic acid determination, amino acid analysis, and/or coumarin fluorescence. Later, when I found that I could not obtain reproducible HPLC elution profiles from the trypsin digestions, I tried to cut up the sodium channel protein using cyanogen bromide (CNBr), a chemical that cuts the protein at methionine residues. Unfortunately, neither method proved successful in generating reproducible HPLC elution profiles." Lewallen WD at 4. Thus, what the grant described as successful techniques resulting in specific bridge locations being identified by multiple methods, Mr. Lewallen portrayed as a series of failed attempts to achieve the first step in the planned identification process.

[12]If Dr. Angelides intended to assert that ORI could not rely on the absence of data to support its charge because the data might have once been in his records and ORI or Baylor lost or destroyed it, his contention again fails. The charge of falsification is not based merely on drawing a negative inference from the absence of supporting data, but on relying on the absence of supporting data as corroboration of the testimony of witnesses, including the experimentalist, that the data never existed. See ORI Br. at 19, n. 15. In that context, it is insufficient for Dr. Angelides to argue merely that ORI failed to prove that the data might not have existed at some earlier time.

position hence was that he had relied on Mr. Lewallen but that, after a thorough review of Mr. Lewallen's notebook, he had concluded that "all of the data" supplied by Mr. Lewallen were "suspect." Record Ex. 32, at 1; see also Record Ex. 37, at 2.

However, later in his brief to the Panel, Dr. Angelides claimed that such data are "indeed found" in Mr. Lewallen's primary record, but without adequate cross-referencing, so that reconstructing the locations precisely is "daunting." Ang. Br. at 23-24. He also argued that the problem in regard to this issue is "NOT the lack of data in Mr. Lewallen's laboratory records but ORI's expert's inability to interpret that data present within Mr. Lewallen's record." Ang. R. Br. at 102 (emphases in original). This position implies that supportive data are extant, if poorly organized. Yet despite his access to Mr. Lewallen's records both before and during the hearing, and the many years during which he has been aware that these assertions in the grants had been challenged, Dr. Angelides did not proffer to this Panel a single item of primary data tending to demonstrate support, even in part, for the location of any disulfide bridge. Strikingly, Dr. Angelides did not even choose to submit as relevant exhibits the large box of HPLC profiles, notebooks, and other materials that were present at the hearing and that Dr. Angelides described as Mr. Lewallen's records. Even well after the hearing when Dr. Angelides argued that data supporting his claims might exist, counsel for Dr. Angelides expressly declined to submit any of the Lewallen notebooks or materials for the record. See Ruling on Outstanding Motions at 4. It is not plausible that, if the data to support the specific locations of several bridges existed and were available to Dr. Angelides, he would be unable to reconstruct at least some demonstration of how some identifications were made.

Both parties agreed that the records of Mr. Lewallen's work in the laboratory do contain many HPLC tracings. The Panel considered the large number of HPLCs produced to be consistent with Mr. Lewallen's testimony that he persistently but unsuccessfully tried to generate replicable useful HPLC results. Dr. Angelides denied that such repetition was necessary and argued that reproducibility was irrelevant since all that was needed was a resolution of peaks sufficient to separate peptides for later analysis or mass spectrometry. He argued that Mr. Lewallen's records show sufficient resolution and the submission of material for mass spectrometry. See Ang. Br. at 36; Ang. R. Br. at 103-04, 126-27. It is not disputed that Mr. Lewallen did elute peptides and attempt mass spectrometry. However, Dr. Angelides offered no plausible explanation (other than an excessively meticulous personality) for Mr. Lewallen's continuing efforts to get better HPLC results, if Mr. Lewallen had, in fact, already succeeded in getting useable data.[13] Further, Dr.

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[13]Dr. Angelides testified that the reason Mr. Lewallen generated over one hundred HPLC profiles, when admittedly a single successful one would suffice for further analysis, was that Mr. Lewallen --

> disassembled the HPLC and was cleaning the parts so that often times these HPLC profiles would change. He generated -- in the very beginning he had some problems generating HPLCs particularly for the digestions. Part of that was compounded by the

(continued...)

Angelides did not present to the Panel any specific HPLC printout of Mr. Lewallen's to show well-resolved peaks that actually contributed to the claimed identifications of disulfide bridges nor any specific mass spectra that were useful in an identification.[14] Mere submission of material from HPLC peaks in an effort to obtain useable mass spectra does not evidence successful identification of any of the claimed disulfide bridges.

Further, Mr. Lewallen's testimony that he never obtained interpretable mass spectra for this project was corroborated by Dr. Gaskell, who was the head of the mass spectrometry facility. He testified that he was aware of Mr. Lewallen's efforts to use that approach to identify disulfide bridges but that Mr. Lewallen "was not successful with this technique." Gaskell WD at 5 (emphasis in original). He further stated, "The samples that Mark Lewallen provided to the mass spectrometry facility produced no good results. The mass spectrometry log book supports the fact that Mark Lewallen's samples did not produce good results." Id.; see also ORI Ex. 1.

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[13](...continued)
fact that, quite frankly, he wouldn't let the instrument alone and so he ran HPLCs after HPLCs. Indeed, if you get good HPLCs you submit the HPLC fraction and mass spec, and it's essentially finished. Again, my opinion is that he would have progressed much further had he not fooled around with the instrumentation that necessitated for him to generate all the HPLCs.

Tr. at 1996. Even assuming that Dr. Angelides is correct that Mr. Lewallen created much of his own difficulty in obtaining consistent HPLC results, the inescapable conclusion is that the only reason that so many HPLC profiles were generated was that Mr. Lewallen did not have confidence that he had obtained a reliable profile that yielded meaningful results on further analysis or on mass spectrometry.

[14]At one point, Dr. Angelides claimed that an HPLC submitted by ORI showed that a "resolvable HPLC" existed from which "fractions were collected." Ang. Reply to ORI's Resp. to Spoliation, at 20, citing ORI Ex. 12. However, this claim is irrelevant since it is not disputed that Mr. Lewallen submitted for mass spectrometry fractions obtained from HPLC. Dr. Angelides did not offer an explanation of what, if any, role this HPLC might have played in identifying any particular disulfide bridge. In his reply brief, Dr. Angelides mentioned ten HPLCs dated between February 1989 and June 1991 that he asserted reflected digestions of sodium channel with trypsin and/or CNBr with well-separated peaks, and some of which he asserted were "noted for collections and submission for amino acid analysis and/or mass spectral analysis." Ang. R. Br. at 42, n.31. He did not offer any of these cited HPLCs into the record so they are not available to the Panel. Further, he did not identify what contribution any of these HPLCs made to locating a particular disulfide bridge or even a cysteine that might be involved in a bridge nor did he connect any of these HPLCs to a resulting amino acid analysis or mass spectra that contributed to such an identification.

Dr. Angelides challenged Dr. Gaskell's testimony on the basis that Dr. Gaskell could not definitively show from the logbook that no results were ever obtained from samples provided by Mr. Lewallen.[15] See, e.g., Ang. Br. at 28-29. Dr. Angelides also argued that ORI based its claims merely on selected entries from the mass spectrometry logbook shown in ORI Exhibit 1.[16]

Dr. Gaskell's testimony was not simply that he reviewed excerpts of the logbook and found no examples of successful mass spectra tied to Mr. Lewallen's disulfide project. Rather, he affirmatively recalled Mr. Lewallen's frustrating results and that he had in fact personally informed Dr. Angelides about it at the time: "I recall discussing the lack of success with mass spectrometry of Mark Lewallen's samples with Dr. Angelides. To my recollection, the samples that Mark Lewallen provided to my facility did not result in useful data. As Dr. Angelides was the head of the lab in which Mr. Lewallen worked, I let Dr. Angelides know of the difficulties with the mass spectrometry of Mr. Lewallen's samples." Gaskell WD at 6. Dr. Gaskell agreed that he could not rule out the possibility that samples from Dr. Angelides's laboratory might have yielded useable mass spectra. Id. He testified that the notation system in the mass spectrometry logbook was designed simply to be sure that each sample had a unique identifier but not to provide complete information itself on the sample, so that he could not be certain about whether any samples not otherwise described might have included sodium channel peptides. Tr. at 334-

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[15]Dr. Angelides argued that the retention of any record of mass spectra results in the computer records demonstrated that those results had "sufficient value and content," since files that did not yield useful results were erased. Ang. Br. at 29; Ang. R. Br. at 126-27. This argument misstates the testimony, which was that files that had yielded no meaningful results might be erased to save computer storage space, but not that only files that had produced good results were retained. See Gaskell WD at 3. Therefore, the mere existence of any records of results of peptide fragments submitted for mass spectrometry by Mr. Lewallen does not contradict the testimony of both Mr. Lewallen and Dr. Gaskell that the results were not useful.

[16]ORI Exhibit 1 consisted only of logbook pages relating to the mass spectra included in Dr. Angelides's grant applications as one of the figures discussed in the next section. Dr. Angelides argued that ORI's exhibit was "selective" and that all records of Mr. Lewallen's samples were relevant. See Ang. R. Br. at App. 2. In response, counsel for Baylor sent a letter to the Panel and parties, dated September 21, 1998, attaching, among other things, what purported to be a photocopy of the entire mass spectrometry logbook for 1990 and 1991. The letter asserted that the original was available at the hearing and that Dr. Angelides's counsel had been so informed before the hearing. We discussed above the merits of Dr. Angelides's claim of spoliation of evidence, but in regard to the mass spectrometry logbook specifically, Dr. Angelides did not present any basis to question that the logbook was among the Baylor materials available to both parties at the hearing or that the photocopy currently in the record is an accurate representation of the original. Nor did Dr. Angelides present any argument that any particular contents of the logbook contained evidence of successful mass spectrometry (as opposed to the mere submission of samples for testing). Cf. Ang. Reply to ORI's Resp. to Spoliation at 8.

39. Nevertheless, he was clear that "the vast majority of samples that derived from Mark Lewallen did not produce useful results." Tr. at 338.

Mr. Lewallen's account was also consistent with the fact that Dr. Angelides presented no mass spectra to the Panel to show a result that supported his claims about disulfide bridges. Dr. Angelides did not deny that Mr. Lewallen's records contain no such mass spectrometry results. However, he argued that there are, in Mr. Lewallen's notebooks, "many entries for samples generated and submitted for mass spectra analysis including a series of control proteins," suggesting that the absence of mass spectra when the notebooks have entries showing submissions was somehow suspicious. Ang. Br. at 41. Such entries, however, would not contradict the assertions of Mr. Lewallen, corroborated by Mr. Gaskell, that Mr. Lewallen made many attempts to get mass spectra of peptides without obtaining successful results, since the mass spectrometry facility did not always retain output that was "completely uninformative" due to computer storage limits. Gaskell WD at 3. In essence, Dr. Angelides's argument was that the evidence that samples were submitted showed that Mr. Lewallen obtained fractions from his HPLC profiles, and that therefore they must have been well-resolved, and that therefore he could have made a tentative assignment of the location of disulfide bridges based on the results of those mass spectra. Ang. Reply to ORI Resp. to Spoliation at 8. Actually, Dr. Angelides suggested that he might have made such assignments in conjunction with Dr. Owen Jones, although Dr. Angelides did not otherwise explain what role Dr. Jones might have had in this process, since he was not the experimentalist whose data were allegedly interpreted. Id. The mere submission of samples with no evidence of positive results will not support this claim. The question at issue is not whether Mr. Lewallen ever obtained fractions from HPLC results and sought to use mass spectrometry, but whether he ever obtained interpretable mass spectra on which Dr. Angelides reasonably relied to assign disulfide bridge locations. Mr. Lewallen and Dr. Gaskell deny this; the records do not show any evidence of it; and, far from confirming that he ever joined Dr. Angelides in reviewing such data to tentatively assign disulfide bridges, Dr. Jones testified that he was well aware of Mr. Lewallen's lack of success on the disulfide project:

> Mark was the only one who knew how to run the HPLC when I joined the laboratory. He was frequently taking apart the machine and cleaning it because he believed that the system was messed up and that was the reason he was getting bad data. Mark did nothing to hide the fact that he was unsuccessful on this project. I think that everyone in the lab knew about his lack of success.

Jones WD at 8.[17] The undisputed evidence that Mr. Lewallen constantly disassembled and recalibrated the HPLC machine further substantiates Mr. Lewallen's assertions that he did not obtain good data from his efforts.

The Panel concluded that primary data do not exist to support any of the claims made about the location of disulfide bridges in the sodium channel.

2. Responsibility for textual claims relating to identification of disulfide bridges

It is not disputed that Dr. Angelides was the principal investigator in each of these grants and that he prepared, signed, and submitted each of the applications. Each application contained a required statement by the principal investigator to the effect that he was aware that willful provision of false information in the application for federal funding was a crime. Dr. Angelides asserted that the information he submitted in his grants was provided by individuals that he "believed to be truthful and accurate at the time" and that he could not do "anything more in terms of preparation of grants" than he had been doing. Tr. at 1583, 1616. He asserted that his practice was to "jointly prepare" grant applications with the experimentalist who conducted the work involved and then to provide "copies to everybody" after submission. Tr. at 1293, 1304.

This testimony conflicted with the statements of most of the members of his laboratory during the relevant period who appeared before the Panel. They described Dr. Angelides as writing and preparing his grant applications alone and rarely providing others with access to them. See, e.g., Elmer WD at 7-9; Jones WD at 3-4; see also Benke WD at 3; Joe WD at 4-5. Consequently, although they might provide data to him on request or he might access data of theirs from their notebooks, laboratory members did not necessarily become aware of how Dr. Angelides had presented that data. Id.; see also Wood WD at 4-5. For example, Dr. Nutter testified that Dr. Angelides "was solely responsible for preparing the grant applications, including the preparation of figures, figure legends and tables that were included in his grant applications" and that, while Dr. Angelides might have used some of his data for that purpose, he "was not asked to review such figures or tables, nor was I told they were being put into a grant application." Nutter WD at

[17]Dr. Angelides attacked Dr. Jones's credibility on the basis that Dr. Jones's testimony had been manipulated by Dr. Berget and Baylor counsel. Ang. Br. at 18-19. Dr. Angelides's brief presented the record on this interaction in a misleading light, implying that Dr. Jones believed he would get a letter clarifying that his own scientific integrity was not in question only if "he came out of the closet" with a "load of dirt," on Dr. Angelides. Ang. Br. at 19. On the contrary, in the cited testimony, Dr. Jones indicated that he understood the reluctance of the attorneys involved to provide such an assurance to him for fear that something might later reveal "a whole load of dirt" on him. Tr. at 515-16. Dr. Jones testified that he asked for and received a letter to establish that the charges in this matter did not call his work into question. Tr. at 509-17. He testified that he did not believe that "what was said was contingent on the letter or vice versa. I mean, it just wasn't." Tr. at 517. He denied that he felt any pressure to alter his testimony. Id. The Panel found Dr. Jones's testimony credible and disinterested.

7. In the same vein, Dr. Velazquez stated his "belief that Dr. Angelides wrote grants alone." Velazquez WD at 2. He testified: "I never assisted Dr. Angelides in preparing any grant applications. He never asked me to review any grant application he was preparing. To my knowledge he was solely responsible for preparing grant applications, including the preparation of figures, figure legends, and tables that were included in his grant applications." Id. Dr. Elmer similarly testified that describing grant preparation in Dr. Angelides's laboratory as a "team effort" is "not consistent with reality." Elmer WD at 8.[18] The Panel concluded that, where the experimentalist was not given an opportunity to review the presentation of his data in a grant application, Dr. Angelides must be held responsible for the accuracy of that presentation.

Mr. Lewallen testified that he was never informed that his results were included in the grants at issue and that he was never asked to review them before submission. Lewallen WD at 8-9. Since the testimony of so many disinterested witnesses supported Mr. Lewallen's position as consistent with Dr. Angelides's normal practice, the Panel found Mr. Lewallen credible on this point. For this reason, the Panel held Dr. Angelides alone responsible for the accuracy of his reporting of his laboratory's results on the disulfide project.

The Panel also considered whether the repetition of claims of success indicated independent responsibility for the accuracy of each claim or might merely represent accidental carryover of errors. Although the grants repeatedly made very similar claims about having identified two or more disulfide bridges, the precise language used and the experimental methods described were not identical from year to year. For this reason, the Panel concluded that each application involved a conscious formulation revising each description to suggest an evolution in results and

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[18]Dr. Angelides asserted that his witnesses established that the laboratory "functioned as a team in grant preparation," but this was not a fair characterization of the cited testimony. Ang. Br. at 15-16. Several witnesses did relate experiences with Dr. Angelides's grant preparation that differed in that they reported more active involvement by senior laboratory members in providing data and even participating in writing grant language or reviewing drafts. See, e.g., Hicks WD at 3-4; Maleic-Jericevic WD at 7-12; Wilkemeyer WD at 2-3. These witnesses generally joined the laboratory later than the relevant time frame. Dr. Hicks came in July 1991; Dr. Maleic-Jericevic in about 1993; Dr. Wilkemeyer in September 1992. None of them had any involvement with the particular grants at issue. While their experience may well have been different, that does not undercut the testimony of other disinterested laboratory members that Dr. Angelides was not so open with all of his grant applications during the period at issue. The only testimony offered by Dr. Angelides that specifically suggested that Mr. Lewallen did play any role in the construction of a grant application was that of Ms. Quezada, a word processing specialist, who testified that Mr. Lewallen (known to her only as Mark), as well as Dr. Wible "would just do tables for the grant and some, on occasion, they would do a figure for the grant, but they never did any of the -- you know, any of the writing for the grant." Tr. at 1222; see also Hearing Ex. 21, at 9-10 (Quezada testimony at Baylor). It was clear that she did not have a specific memory of the particular contributions of these individuals. Her testimony did not contradict Mr. Lewallen's assertions that he did not write any of the text in the grants at issue.

methods used. The Panel concluded that Dr. Angelides was responsible for inserting the claims consciously in each application rather than having simply carried over erroneous language from the first grant application in which it appeared. (We address later in this decision whether he was aware the claims were false when he included them; here, we conclude simply that he made an independent decision to prepare and include each challenged claim.)

In addition, the Panel noted that Dr. Angelides alone was in the laboratory throughout the period during which these grants were prepared and submitted and that he continued to make claims of success in this project in grant applications even after Mr. Lewallen had left his laboratory. The assertions quoted above in the GM48816-01 grant in 1992 are substantively different from the language in any of the preceding grants. Even had he obtained the information in earlier grants from Mr. Lewallen, Dr. Angelides alone was responsible for the assertions made in the GM48816-01 grant because that was submitted well after Mr. Lewallen's dismissal from the graduate program and departure from the laboratory. In his testimony before the Baylor Sub-Committee, Dr. Angelides explained that he kept using the same claims from Mr. Lewallen's work in multiple grant applications because they were only preliminary data and no one else in the laboratory was available to confirm or re-examine his results. Record Ex. 17, at 90. By the time he submitted the 1992 grant, however, Dr. Angelides should have been alerted to the need to confirm claims about success in this project, especially in light of Mr. Lewallen's lack of any defense at the meeting of the thesis committee when he was dismissed. Dr. Angelides retained access to all of Mr. Lewallen's records. The GM48816-01 grant claimed precise locations of two bridges and enumerated the total number of cysteines involved in bridges, so that the presentation went well beyond general preliminary information.

The Panel concluded that such specific claims of success were not equivalent to a situation in which a grant application might contain preliminary interpretation of early data in support of claims that proved through later experimentation not to be ultimately supportable or reproducible. The situation here rather is that Dr. Angelides persisted in repeating claims without ascertaining that any actual data (preliminary or otherwise) ever existed on which these claims were based. In this situation, he cannot evade responsibility by arguing that the claims were intended to be tentative or preliminary, or that he lacked resources to verify them further, because he did not demonstrate that he had real data on which to found the claims initially. While the presentation of preliminary results in a grant application may not require the same level of demonstrated reproducibility called for in a published paper, Dr. Angelides offered no basis on which to conclude that the signatory of a grant application is not responsible for telling the truth about those results that are reported, and the Panel received testimony to the contrary. Thus, Dr. Gilbert testified that even preliminary data, if falsified, can significantly distort the evaluation of the merits of a proposal and undercut the fairness of the peer review system of grant review. See Tr. at 95 (Gilbert).

3. Intentionality of false claims relating to identification of disulfide bridges

Dr. Angelides argued that, in any case, any erroneous claims about the disulfide bridges were the result of his good faith reliance on the representations made to him by Mr. Lewallen, and therefore, even were he responsible for their inclusion, he did not intentionally make false claims. He further argued that he had no reason to lie about progress in this project, since the claims were not fundamental or required parts of the grant applications.

Overall, the Panel found Dr. Angelides's position about the way Mr. Lewallen allegedly conveyed to him the information that was presented in the grants unclear and shifting. At times, he asserted that Mr. Lewallen misled him by telling him falsely that the project had had success, while at other times he argued that data existed that supported the accuracy of the claims. Dr. Angelides testified before Baylor that he relied largely on verbal communications from Mr. Lewallen but that he was also shown a variety of data, particularly HPLCs, that led him to assume that at least some preliminary evidence supported Mr. Lewallen's interpretations. Record Ex. 21, at 79-82. Dr. Angelides specifically said, however, that he did not recall seeing any sequencing data or anything in writing from Mr. Lewallen identifying any two specific cysteines involved in a disulfide bridge. Id. at 80-81. It is difficult to see, based on Dr. Angelides's own descriptions of the sort of detailed, correlated data that would be necessary to support these claims and the specificity of the locations reported, how oral reports and viewings of various HPLC profiles could have been an adequate foundation on which to base the expansive claims of these grant applications.

The testimony of Dr. Angelides and Mr. Lewallen was in direct conflict about whether Mr. Lewallen led Dr. Angelides to believe that any disulfide bridges had been located. The Panel therefore considered which testimony was more credible and concluded that Mr. Lewallen's testimony was more credible. Mr. Lewallen's testimony was consistent from the beginning of the Baylor investigation through the hearing before the Panel, was supported by the documentary record, was corroborated in numerous respects by other neutral witnesses, and was consistent with his conduct regarding his dismissal from the graduate program. On the other hand, Dr. Angelides's testimony was vague about the basis for his belief that Mr. Lewallen presented him with information sufficient to justify the inclusion of these claims in his grant applications, was not supported by any primary data or other documentation, was in conflict with the testimony of other witnesses, and was inconsistent with his actions in seeking Mr. Lewallen's dismissal from the graduate program.

First, Mr. Lewallen has steadfastly denied any success in locating disulfide bridges. In his testimony before the Baylor Sub-Committee, as before this Panel, Mr. Lewallen consistently denied that he had ever achieved or claimed to achieve virtually any of the steps reported as accomplishments in the grant applications. See, e.g., Record Ex. 21, at 105 (Baylor testimony on November 1, 1993) ("The primary project I was working on in the laboratory was the disulfide project. Every strategy which I had utilized to try and get the information did not work. This was over a period of five or six years."). He testified, as discussed in regard to the extant primary data, that he made many attempts to obtain interpretable data in this project with very little success. Lewallen WD at 4-7. He testified, for example, that he was never able to obtain

reproducible results from HPLC separation, which, he testified, would have been an essential first step. Lewallen WD at 4. When he was unable to get reproducible results using trypsin digestion, he attempted to use cyanogen bromide (CNBr), also without success. Id. Thus, rather than simply a less laborious alternative method as claimed in the GM48816-01 grant, the change to CNBr was part of a continuing effort to find some workable methodology. Mr. Lewallen also tried changing digestion conditions and attempted to use mass spectrometry but obtained no useable results. Lewallen WD at 5-7.

Not only did Mr. Lewallen testify that he never succeeded in achieving the final results claimed in the grants (in terms of identifying the number and location of disulfide bridges), he testified that much of the detailed information presented about the methods that had purportedly been used to achieve these results was wrong, because he had never even used those approaches, much less achieved success with them. Thus, for example, he testified that he never tried to use in vitro translated sodium channel with [^{35}S]-Cys as a tracer, despite language in several grants presenting this approach as having been used successfully and having resulted in translated protein that was "full length, functional, and contains sufficient ^{35}S-Cys in order to serve as a tracer for identification of those peptides linked by disulfide bonds." Lewallen WD at 12; see, e.g., Record Ex. 3, at 7 (NS01218-03) and Record Ex. 9, at 22-23 (NS24606-05); see also Taylor WD at 9. He stated that this "methodology was proposed to me by Dr. Angelides as a second potential means of accomplishing the disulfide project. However, to my knowledge this proposed methodology was never attempted." Lewallen WD at 12.[19]

Secondly, as discussed above, the documentary record is devoid of any evidence that data supporting the claimed locations of disulfide bridges ever existed. The absence of such data is consistent with Mr. Lewallen's claim that no success was ever achieved. It is also consistent with an intentional misrepresentation. It is less likely that simple error or optimistic overinterpretation could account for claims of having located disulfide bridges in the absence of any relevant data than if some data existed even if insufficient to reach the specific identifications assigned.

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[19]Dr. Angelides argued that Mr. Lewallen's notebook contained a record of an experiment using radioactive N-ethylmaleimide (NEM), contrary to Mr. Lewallen's testimony that he "never utilized sodium channel proteins labeled with radioactive cysteine or labeled with radioactive N-ethylmaleimide, and . . . never submitted radioactive samples for microsequencing." Compare Ang. Br. at 25-26 with Lewallen WD at 13. Mr. Lewallen testified that he did discuss the possibility of this approach with Dr. Angelides and that he "ordered this chemical and did some calculations about the feasibility of the experiment, but . . . never performed the experiment with radioactive NEM." Lewallen WD at 13; see also Tr. at 1133 (Lewallen). Dr. Angelides did not provide for the record the entry from Mr. Lewallen's notebook that he claimed showed actual experimentation with, rather than merely feasibility calculations concerning radioactive NEM. The Panel inferred that the documentation did not support Dr. Angelides's claims.

Third, by all accounts, including his own, Dr. Angelides was closely involved in Mr. Lewallen's work. Tr. at 1486-88, 1977-78 (Angelides). Dr. Angelides stated that the record shows that he "had frequent meetings with Mr. Lewallen to monitor his progress in each of his projects." Ang. Br. at 32-33. Mr. Lewallen testified that Dr. Angelides was "intimately familiar with" and "directed every step of my research," so that "he knew exactly what was going on." Tr. at 2088; see also Lewallen WD at 4-5. In general, his laboratory members portrayed Dr. Angelides as well aware of the work of his staff and as active in reviewing their data and results, and as particularly so with regard to Mr. Lewallen. See, e.g., Velazquez WD at 2-3; Wood WD at 4; Lewallen WD at 4-5. The Panel did not find it believable that Mr. Lewallen could have misled Dr. Angelides for almost four years about achieving success in locating these specific disulfide bridges. Dr. Angelides himself, as mentioned above, pointed out that documenting the location of a bridge would have meant generating and cross-referencing a variety of data. Had Mr. Lewallen made such claims, it seems implausible that Dr. Angelides would have accepted them over such a long time without having seen the supporting data. Yet, Dr. Angelides's claims that Mr. Lewallen showed him HPLC, mass spectrometry, and amino acid analysis results are not supported by a single example of data in Mr. Lewallen's records and conflict with the testimony of Dr. Gaskell, Mr. Lewallen, and others. Cf. Tr. at 1475, 1486-87 (Angelides).

Fourth, the uniform testimony of the laboratory members was that Mr. Lewallen was open about his lack of success in this project. The record indicates that the entire laboratory was aware of Mr. Lewallen's failure in regard to this project and of Dr. Angelides's frustration with Mr. Lewallen over this failure. For example, Dr. Jeffrey Wood testified that it was his "opinion that everybody in the laboratory knew that Mark was not having any success with his experiments with the disulfide bridge and other projects, including Dr. Angelides." Wood WD at 3. Dr. Velazquez, who shared a bench with Mr. Lewallen, testified that he knew Mr. Lewallen "was not successful in mapping disulfide bridges" and believed "that was the reason that Dr. Angelides had him leave the lab." Velazquez WD at 3. It is illogical that Mr. Lewallen would falsely tell Dr. Angelides that he had identified specific disulfide bridges and then repeatedly share his frustration over his lack of success with others in the laboratory, and implausible that Dr. Angelides would have uncritically accepted such representations without insisting on documentation. Dr. Jones, who was in the laboratory from 1987 to early 1991, testified that Dr. Angelides knew of Mr. Lewallen's failure:

> Dr. Angelides was aware of Mark's lack of progress. I often heard Dr. Angelides reproaching Mark in Dr. Angelides' office. I was also aware of Dr. Angelides' familiarity with Mark's progress because I once made a suggestion to him that Mark might have more success if he used eel electroplax rather than rat brain in his project to map the disulfide bridges in the sodium channel. I said this because eel tissue is easier to work with than rat brain, as there is significantly more protein in the sodium channel preparations from eel. Dr. Angelides indicated that he did not want Mark to switch from rat brain. He commented that Mark should have been able to do the project with rat brain and that he was unhappy with Mark's lack of success.

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> Mark certainly never gave me any idea that he had success with the HPLC or mass spec in terms of this project. It was my impression that Mark's research had stalled at the level of trying to get good HPLC profiles. He never told me that he had identified certain cysteines that were linked in an extracellular loop. He also never told me that he had located one, two or three of the disulfide bridges in the sodium channel. We were colleagues at the time and frequently discussed our work. If he were claiming success in the disulfide project, he would have told me and others in the lab. It seems outrageous to me that Dr. Angelides would put those claims in his grant when everybody, including Dr. Angelides, was aware that Mark Lewallen was having severe problems with even the early stages of the disulfide bridge project. If Mark had found those specific cysteines and had located the disulfide bridges claimed in the grants, then I do not believe Dr. Angelides would have told Mark to leave his lab.

Jones WD at 7-9.[20]

Dr. Angelides argued that ORI did not show that Mr. Lewallen made presentations to the thesis committee or laboratory in which he announced his failure and substantiated it by showing "poor HPLCs or non-interpretable mass spectra." Ang. R. Br. at 111. The absence of a formal laboratory presentation by Mr. Lewallen is consistent with the absence of any evidence that he had any interpretable data to present. In regard to the thesis committee, Mr. Lewallen testified that he consulted with Dr. Susan Hamilton, who served on his thesis committee, for advice about the technical difficulties he encountered in this project. Lewallen WD at 5. Dr. Hamilton corroborated that he sought her advice several times and affirmed that both the committee and Dr. Angelides were aware of the failure. Hamilton WD at 4-5. Since Mr. Lewallen continued to work on this project until Dr. Angelides decided to dismiss him, it is logical that Mr. Lewallen did not announce final failure in earlier statements. Moreover, Dr. Angelides has produced no corroborating evidence that Mr. Lewallen ever made any statement or presentation to anyone else besides Dr. Angelides even suggesting that he had identified a single disulfide bridge or had any other success in achieving any of the steps claimed in the grant applications. The Panel found

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[20]Dr. Angelides also contended that those who testified from his laboratory that they were aware of Mr. Lewallen's failure should be discounted because they had little "overlap or interactions" with Mr. Lewallen. Ang. Br. at 27. The Panel did not find this argument persuasive. The laboratory members involved did not report merely that they did not hear of successes by Mr. Lewallen but rather several clearly recalled Mr. Lewallen's vocal frustration at repeated failure, and Dr. Angelides's explosions of anger with Mr. Lewallen over the lack of results. For example, Dr. Jones testified that Dr. Angelides would "blow Mark up" from time to time, meaning he "was so dissatisfied with Mark's progress on various occasions that he would have him in the office -- invariably in the office, and those of us who were in the lab could hear it. I could hear him detonating Mark. I mean, he basically . . . lambasted Mark." Tr. at 534-35.

that the testimony of laboratory and thesis committee members that Mr. Lewallen's lack of success was widely known and bemoaned was credible, and was not undercut even if Mr. Lewallen did not attempt to publicly or formally document failure.

Fifth, had Dr. Angelides in fact accepted claims of success from Mr. Lewallen such as those reported in these grant applications, then Dr. Angelides's behavior in regard to Mr. Lewallen's doctoral program is inexplicable. The Panel received testimony from Dr. Hamilton that Dr. Angelides cited Mr. Lewallen's lack of progress in this particular project as a basis for his dismissal. Hamilton WD at 4. She testified that Mr. Lewallen did not attempt to mislead the committee about his progress:

> As a member of Mr. Lewallen's thesis committee, I knew that he was not having much success with this project. He never claimed to have mapped the locations of any disulfide bonds in the sodium channel to his thesis committee. All the members of Mr. Lewallen's thesis committee should have been aware that he hadn't had success on this project of mapping the disulfide bridges in the sodium channel.

Hamilton WD at 4. Dr. Angelides responded that he did not dismiss Mr. Lewallen for failing in this particular project but rather for failure to bring any project to completion. Tr. at 1294-96; Ang. Br. at 32-33. Even if a lack of closure was the underlying reason for Dr. Angelides's dissatisfaction with Mr. Lewallen, the Panel did not find it plausible that Mr. Lewallen would accept this criteria so fully as to omit even to point out to his thesis committee that he had, nevertheless, made substantial progress in this major portion of his work (to the point of having identified exactly how many of the cysteines in the protein were involved in bridges and where specific bridges were located). Logically, any graduate student in such a situation would have more motivation to stress than to understate any successes to a thesis committee. Yet, Dr. Hamilton testified that Mr. Lewallen sat "very quiet" during the final meeting of his thesis committee, and that he "never claimed any progress relating to any of his projects, including the project to map the disulfide bridges in the sodium channel." Hamilton WD at 5-6. Consequently, Dr. Hamilton testified that, "[b]ased on Dr. Angelides' claims that Mr. Lewallen had not made adequate progress and the fact that Mr. Lewallen did not challenge this assertion, the thesis committee determined that Mr. Lewallen would be dismissed from the graduate school." Id. The Panel concluded that, had Mr. Lewallen had any significant progress to report and had he provided evidence of such progress to Dr. Angelides for use in recent grant applications, even if Dr. Angelides deemed it less than adequate for a doctorate, Mr. Lewallen would still have attempted to highlight it to his thesis committee in a progress report or the final meeting. Clearly, the opinion of Mr. Lewallen's co-workers in the laboratory was that such evidence of progress would have been likely to forestall his dismissal from the graduate program. See, e.g., Velazquez WD at 4; Jones WD at 7. Mr. Lewallen's silence, even in the face of imminent dismissal, is thus inconsistent with his having made the claims that Dr. Angelides was including in the grant applications.

Dr. Angelides argued nevertheless that Mr. Lewallen did make some claims of success to the thesis committee, citing to a November 20, 1989 progress report. Record Ex. 45, at Att.III.114. However, the language of the progress report supports precisely the opposite conclusion. Id. Mr. Lewallen wrote that "[d]etermining the disulfides in the NaCh protein has been an ongoing methodological problem which is finally coming to fruition." Id. at A-200-07. Plainly, this report puts the best face on an acknowledgment that the project has been stalled in technical difficulties, the resolution of which is only then promising to yield results. Even this was characterized by Dr. Hamilton as "overly optimistic" since Mr. Lewallen still did not have successful results "a year later." Tr. at 262-63 (Hamilton). Yet this report was submitted at a time well after Dr. Angelides had already claimed in multiple grant applications to have located three or more bridges.

In light of the factors enumerated above, the Panel did not find credible Dr. Angelides's testimony that he had "simply reported the progress that had been communicated" to him by Mr. Lewallen in making the claims of success in this project. Tr. at 1482 (Angelides). While a principal investigator must indeed place some reliance on laboratory members to provide and interpret their data, the situation found by the Panel here is one where the principal investigator, faced with a persistent and frustrating failure by a laboratory member to achieve the anticipated results, nevertheless chose to report success.

Further, the Panel found that the claims made in the grant applications that disulfide bridges had been located and identified using several different methods clearly enhanced the portrayal of the accomplishments and capacities of Dr. Angelides's laboratory. In his 1993 testimony before the Baylor Sub-Committee, Dr. Angelides stated that he was not aware of any laboratory that, even as of then, had published identifications of disulfide bridges in the sodium channel. Record Ex. 21, at 82-83; see also Taylor WD at 25. The competitive applications themselves each present the determination of the profile of the sodium channel disulfide bridges as one of the specific aims for the proposed funding. See Record Ex. 10, at 19; Record Ex. 13, at 12. The career grant applications, while not competitive, set forth a record of accomplishment to justify continued support, and the work on determination of the disulfide bridges is prominently featured in each application as evidence of progress during that budget year. See Record Ex. 3, at 7-8; Record Ex. 4, at 7-8; Record Ex. 5, at 7. Therefore, Dr. Angelides had a motive to overstate his laboratory's achievements in seeking funding for further work on this project by making it appear that he had shown a promising lead in elucidating the structure of the sodium channel through identifying disulfide bridges.

Dr. Angelides disputed this conclusion on the basis that ORI had not proven that "the statements on the progress of the disulfide project were fundamental" to the funding of the grants or "clearly required" or that the omission of the claims "would have severely compromised" his applications. Ang. Br. at 31. He also argued that the nature of the project continuation and career development awards did not support a finding that the misrepresentations could have been intended to influence the funding. Id. He cited no authority to support his contention that it is a necessary element of scientific misconduct that the false statement be obligatory or fundamental

to the funding proposal, and the Panel has found no such authority. Cf. id. Clearly, statements tending to show progress toward the stated specific aims of the grant application and to assert the achievement by the laboratory of accomplishments not published by any other laboratory in the field are relevant to the funding decision, and, if false, are more likely to be intentionally so than an erroneous statement which tended to cut against the interests of the applicant. Although Dr. Angelides argued that ORI had not established a standard for reporting work in a continuing or career application at the time, he himself expressed a standard: "One simply reports the progress on the project that has occurred." Ang. Br. at 31. Applying that standard, the Panel found that Dr. Angelides failed to meet it. Instead, he reported progress that had not occurred.

Based on the considerations discussed above, the Panel concluded that the misrepresentations in the listed grant applications were not the result of unintentional error or good faith reliance on erroneous information received from Mr. Lewallen. Instead, the Panel concluded that the preponderance of the evidence supported the conclusion that Dr. Angelides acted intentionally in presenting claims he knew to be false.

Dr. Angelides also suggested that the assertion that 12 of the 38 cysteines in the sodium channel were involved in disulfide bridges might have rested not on Mr. Lewallen's work but on experiments conducted in 1986 by another graduate student of his while he was in Florida, Dr. Thomas Nutter. See Ang. Resp. to Baylor at 202; Tr. at 1490 (Angelides) ("The original information and the performance of these experiments were conducted by Mr. Nutter. There is no doubt about it, that the initial experiments were conducted by Mr. Nutter, despite what we may have heard."). Dr. Angelides testified that Dr. Nutter's role was documented in records in the possession of Baylor. Ang. Resp. to Baylor at 202; Tr. at 1687-88 (Angelides). Dr. Angelides proffered an excerpt from Dr. Nutter's laboratory notebook in support of this claim. Record Ex. 45, at Att. III.108. Dr. Nutter's work was on sodium channel in electric eel rather than rat brain and his notebook pages describes an experiment attempting to determine disulfide bridges using N-ethylmaleimide which would "theoretically . . . label all cysteines not involved in disulfide bridges." Id. at p. A159. Dr. Nutter testified that the protocol reflected in this excerpt was for an experiment that failed. Nutter WD at 4-5. He was not in fact able to determine either the total number of cysteines or the number involved in disulfide bridges in this experiment, and he never attempted to do so on any other occasion. Id. He testified that the predicted number of cysteines in the eel sodium channel based on the clone's gene sequence was only 36 and that he never told Dr. Angelides that 12 out of 38 cysteines were involved in disulfide bridges. Id. The Panel reviewed Dr. Nutter's notebook and found that his testimony was credible and consistent with his records. Hearing Ex. 3.

Dr. Angelides also pointed to statements in his response to the deferral of his grant application NS24606-05 to demonstrate that he was not making intentionally false claims of success in this project, since he had reported problems to NIH. Ang. R. Br. at 30; Record Ex. 11 (original grant application at Panel Ex. 5). In the deferral submission, he stated that the work had been "a very difficult biochemical project" and "labor-intensive," but that he continued to be "very strongly committed" to it as a way of clarifying the tertiary structure of the protein independent of the

competing models. Id. at 9-10. He proposed an "alternative strategy" and suggested that, depending on the secondary structure of the protein, a disulfide might also be formed between two specific segments "[i]n addition to the disulfides we have tentatively assigned." Id. at 10. Dr. Angelides was not charged with misconduct in connection with statements about disulfide bridges in this deferral submission. The grants in connection with which he was charged with misrepresenting the status of this project contain no similar qualifying language indicating that the identifications are preliminary or tentative, but rather present them as accomplished results. Furthermore, Dr. Angelides presented no data or other evidence providing any basis whatsoever for even a preliminary judgment as to the location of disulfide bridges.

Dr. Angelides also argued that he should not be held responsible for the false statements in the grant applications because Dr. Brown, as department head, "independently prepared and signed the sponsor's statement" on grant application NS01218-05 in 1991. Ang. Br. at 31. The sponsor's report included an assertion that, within the past year, Dr. Angelides had "determined some of the disulfide bridges of the Na+ channel by mass spectrometry." Record Ex. 5, at 13. Dr. Angelides did not present testimony from Dr. Brown to clarify the basis or source for his statement. Dr. Brown's sponsor reports in prior career development applications at issue did not remark on the disulfide bridges despite claims in those applications as well that three or more bridges had been determined. Record Exs. 2, at 8, 13; 3, at 7-8, 13; 4, at 7-8, 15. It is not relevant to the deliberations of this Panel whether Dr. Brown made adequate efforts to verify the progress which he confirmed as sponsor. Regardless, Dr. Brown's signature does not relieve Dr. Angelides of the responsibility for reporting accurately the state of work in his own laboratory when seeking further funding.

5. Conclusion on textual claims about disulfide bridges project

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that the textual claims made in the listed grant applications were false and not supported by the data in the record and that Dr. Angelides was solely responsible for the inclusion of these claims in the grant applications.

C. <u>Presentation of HPLC and mass spectrometry data in figures</u>

In addition to the textual claims about the status of the disulfide bridges project, Dr. Angelides included data in two grant applications purporting to illustrate the results that his laboratory had obtained. In GM48816-01, submitted on January 31, 1992, Dr. Angelides presented as Appendix Figure 2A an HPLC tracing labeled as a "[r]epresentative and typical HPLC profile on CNBr-digested NaCh." Record Ex. 13, at A-2. Dr. Angelides was charged with falsifying the description of Figure 2A in that it was not "representative and typical" of CNBr-digested sodium channel and that it was not the source of peptides for the mass spectrum shown in Figure 2B. ORI Findings # 1-B, at 13. The same HPLC tracing had been included earlier in the Appendix to grant application NS24606-05 in June 1989 as Figure 1 and in the submission in December 1989 in response to the deferral of NS24606-05. In those submissions, although the profile was

identical, the label identified it differently, as a "[r]epresentative and typical HPLC profile on trypsin-digested NaCh." Record Ex. 9, at A-2, and Record Ex. 11 at A-2 (emphasis added).

In addition to the HPLC tracing, the GM48816-01 application included as Appendix Figure 2B a mass spectrometry result purporting to be of a fraction at 60.36 minutes and described in the text as an analysis of peptides from a peak resulting from the HPLC separation of the CNBr-digested sodium channel shown in Figure 2A. Record Ex. 13, at 14, A-2. This mass spectrometry trial did not appear in the earlier grant applications. Dr. Angelides was charged with intentionally falsifying the description of the mass spectrum in three ways: (1) in that it was not from a sodium channel peptide of Mr. Lewallen's but rather from a conantokin-G peptide of Dr. Owen Jones; (2) in that it was not a mass spectrum from the specific fraction taken from the HPLC in Figure 2A; and (3) in that it was not "representative" of mass spectra results obtained in the disulfide bridges project. See ORI Findings #1-C, at 17.

It is undisputed that the data in both figures are not what they purport to be. The central issue as to these figures is whether, as Dr. Angelides argued, Mr. Lewallen provided these data to him, and either orally or in writing led him to believe that they were in fact what the grants represent them to be, or whether Dr. Angelides on his own presented them in the grants in a way that he had to know was false.

1. Primary data relating to HPLC and mass spectrometry data in figures

Mr. Lewallen testified that the HPLC profile in Figure 2A was actually a composite of two overlaid tracings of sodium channel digested by trypsin. Tr. at 1139-40, 1149-50. The component tracings are in the record and were dated May 12 and May 17, 1989. ORI Ex. 12.

Figure 2B is labeled OWEN JONES PEPTIDE FRAGMENT RI-31, dated October 19, 1990. Record Ex. 13, at 14, A-2. It is not contested that the data shown were actually from a digestion of an unrelated peptide fragment of conantokin-G by Dr. Owen Jones, whose research was not involved in the disulfide bridges project. Dr. Jones confirmed the identity of these data. Jones WD at 10.

2. Responsibility for the presentation of these HPLC and mass spectrometry data

As discussed in the prior section, the weight of the testimony was that Dr. Angelides generally prepared his grant applications without review by other laboratory members whose data were presented in them. Where a laboratory member's data were presented but the presentation was not reviewed by the actual experimentalist, the Panel concluded that Dr. Angelides bore a greater responsibility to show a reasonable basis for his presentation of those data, given that he had chosen to dispense with the check on accuracy that would be provided by the experimentalist's review. In the case of GM48816-01, Mr. Lewallen expressly denied that he provided these data to Dr. Angelides to be included in any grant application, and, in particular, that he played any role in preparing or reviewing the presentation of his data in this grant. Lewallen WD at 18, 25.

He contended that he was not included in grant preparation while he was in the laboratory and certainly not involved after he left in September 1991, which was well before the GM48816-01 grant was submitted on January 30, 1992. Lewallen WD at 25

Dr. Angelides disputed Mr. Lewallen's testimony, arguing that Mr. Lewallen had admitted that he provided the data for this grant, which was actually prepared before Mr. Lewallen left the laboratory. Ang. Br. at 33, 37. Dr. Angelides argued that Mr. Lewallen "readily acknowledges in testimony . . . that he created the composite HPLC profile and provided this to Dr. Angelides for use in his grant application . . . together with a detailed description of the methodology." Ang. Br. at 33; see also Record Ex. 33. The cited testimony of Mr. Lewallen does not support Dr. Angelides's characterization. Mr. Lewallen indeed testified that he produced two HPLC profiles and overlaid them to create the composite used in the figure and that he prepared a write-up for Dr. Angelides of the protocol he used to perform tryptic digests of the sodium channel. Tr. at 1139-40. However, Mr. Lewallen nowhere testified that he provided these materials to Dr. Angelides for use in any grant application. See also Tr. at 1163-65, 2091-92. In fact, he denied that he ever knew that they would be used in a grant application and testified that he never saw the grant applications in which they were included until the Baylor investigation. Tr. at 1164.

Instead, Mr. Lewallen asserted that he did prepare and provide the composite HPLC profile to Dr. Angelides, but for a purpose unrelated to its presentation in the grant applications. Tr. at 1163-64, 2091-92. As discussed in the preceding section, Mr. Lewallen testified that his work on this project was stalled by his failure to obtain reproducible HPLC profiles from which to obtain peptides that would produce useable mass spectra. In this context, Mr. Lewallen explained that he created the composite HPLC to illustrate two points: that he had begun to obtain results that were promising but that, even so, the profiles of a single preparation still did not coincide completely. Tr. at 2091-92 (Lewallen). Thus, he testified that, when he looked at these two profiles together, he felt "a mild joy," because the tracings "looked like what I envisioned a profile would look like," so he used the composite to show Dr. Angelides "the fact that it was working, and yet there were differences between the two runs with the same sample." Id.

Dr. Angelides argued that this explanation was implausible because reproducibility was not necessary to the project and because producing a composite HPLC by photocopying was impossible due to "the opacity of the HPLC paper and faintness and problematic copying of red ink of the HPLC printer." Ang. Br. at 34. Yet, Dr. Angelides offered no alternative explanation for the plain fact that the composite tracing exists and was used by him in multiple grant applications, nor did he explain how the difficulty in photocopying was pertinent to the issue of false identification.[21]

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[21]Dr. Angelides also pointed out, as was also noted before the Baylor Sub-Committee, that simple photocopying would have produced several overlaid lines of file descriptions from those which appear on the left side of each of the original tracings. Ang. Br. at 34; Ang. Ex. 20, at 167-68. Those notations do not appear on the composite, and, instead, a single descriptive line

(continued...)

Dr. Angelides's position about the form in which Mr. Lewallen allegedly provided the data to him for the HPLC figure has been inconsistent. In a letter to the Baylor Sub-Committee, dated February 10, 1993, Dr. Angelides stated that Mr. Lewallen gave him "the composite Figure 2A/B and the very detailed methods accompanying this Figure." Record. Ex. 30, at 4-5. Yet when questioned further by the Baylor Sub-Committee about these prior statements that Figure 2A, along with the mass spectra in Figure 2B, was "supplied with figure legends in toto" by Mr. Lewallen, Dr. Angelides said he had been "misunderstood." Record Ex. 17, at 104 (Sept. 9, 1993 testimony of Dr. Angelides before Baylor). He explained as follows:

> [W]hen I say "in toto," I told you about how things were edited, of course. So, people would give me the data and they would identify it. They would say, this is panel such and such. . . . These two were identified by Mark Lewallen as an HPLC, and you're absolutely right . . . that they're identical. [referring to the HPLCs in Fig 1 of NS24606-05 and Fig 2A of GM48816-01] At that time it was unbeknownst to me. But this was identified . . . as the figure that corresponds to this by Mark Lewallen. Now, who physically put this together, I physically put this together. If you're asking that. But on the basis of what he had actually indicated was the correct ones."

Id. at 105 (emphasis added). The implication of this testimony is that Mr. Lewallen did not provide the data in the form of a completed figure but rather that Dr. Angelides prepared the final figure, relying on oral information from Mr. Lewallen as to the identity of the data.

In his brief, Dr. Angelides argued that the HPLC profile was actually first provided to Dr. Angelides by Mr. Lewallen in June 1989, along with the protocol describing the trypsin digestion process.[22] Ang. Br. at 37. However, the June 1989 grant did not include the mass spectrum shown in Figure 2B, so presumably the data could not have been originally presented to Dr. Angelides in the form of a composite Figure 2A/2B. The Panel found that Dr. Angelides's inconsistent descriptions of the form in which Mr. Lewallen initially provided this material to

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[21](...continued)
appears on the right including the date of May 17, 1989. Neither Dr. Angelides nor Mr. Lewallen provided an explanation for the excision of the original descriptions and the insertion of the single line in the composite, although it would not be difficult to cover the description lines in copying.

[22]Although the legend to Figure 2A in GM48816-01 referred to CNBr-digested sodium channel, the same protocol discussing sodium channel preparation and trypsin digestion was attached as in the NS24606-05 application. Compare Record Ex. 9, at A-3 with Record Ex. 11, at A-3. Dr. Angelides suggested that this "discontinuity" would have been obvious to any reviewer of GM48816-01, but did not explain why he himself did not recognize or question it. Ang. Br. at 38.

him supported a conclusion that Dr. Angelides was himself responsible for how he presented it in his grants.

Dr. Angelides also argued that Mr. Lewallen should be held responsible for the presentation of Figures 2A and 2B in GM48816-01, despite its submission after Mr. Lewallen's departure from the laboratory, on the grounds that the grant application was actually prepared in May 1991 (before Mr. Lewallen's departure) but not submitted to NIH until 1992 because Dr. Angelides had not completed it in time for an October 1, 1991 deadline. Ang. Br. at 37-38; Tr. at 1495 (Angelides). Dr. Angelides's position that Mr. Lewallen was still in the laboratory when GM48816-01 was prepared (and therefore that he could have provided Figures 2A and 2B for that grant) was also inconsistent with prior testimony by Dr. Angelides before the Baylor Sub-Committee. Thus, when asked whether he had shown Mr. Lewallen the presentation of his data in that grant, Dr. Angelides first said that Mr. Lewallen must have seen it either during the actual writing or after the grant had been assembled, but then when asked if he recalled the specific circumstances in which Mr. Lewallen reviewed the presentation in the GM48816-01 grant, Dr. Angelides stated that "as you know . . . GM48816 was prepared after he had departed. So there was no opportunity for him to see that." Record Ex. 21, at 50-52 (Nov. 1, 1993 testimony before Baylor) (emphasis added). The Panel did not find credible Dr. Angelides's present argument that Mr. Lewallen reviewed the inaccurate presentation of these data in the GM48816-01 grant.

As to the mass spectrum in Figure 2B, Mr. Lewallen denied that he ever even had possession of these data, which derived from Dr. Jones's work on another project with Dr. Angelides that was unrelated to the disulfide bridges of the sodium channel. Tr. at 2092. He testified that he saw it first during the Baylor investigation. Lewallen WD at 24.

Dr. Angelides claimed that the mass spectrum shown in the figure derived from a sheet containing four mass spectra that he found in a folder labeled "Disulfide Bridges" which he attributed to Mr. Lewallen. Record Ex. 17, at 105 (Sept. 9, 1993 testimony of Dr. Angelides before Baylor). Dr. Angelides admitted that the only handwriting on the folder was his own, but said that the folder was part of the data records compiled by Mr. Lewallen at Dr. Angelides's request in May or June 1991 before Mr. Lewallen left the laboratory. Id. at 94, 105-06.[23] He testified that Mr. Lewallen gave him the sheet of four mass spectra, although Dr. Angelides did not remember what Mr. Lewallen told him about the data, but when asked specifically where the mass spectrum for Figure 2B came from, Dr. Angelides testified: "Oh, that was totally Mark Lewallen's. He gave that totally to me." Id. at 95-96. In later testimony, Dr. Angelides asserted

[23]The remainder of Dr. Angelides's testimony before the Baylor Sub-Committee that day, however, obscured whether his position was that Mr. Lewallen actually put the folder together or whether Dr. Angelides himself put the folder together when Mr. Lewallen left: "So, if you're asking whose handwriting that is, that's my handwriting on those [the folders]. They were compiled by Mark shortly before he left. You know, we all have people when they leave the laboratory, we ask them for the data. So we put it in folders, like I put it in folders, and then we put it together all in notebooks and we put it on the shelf." Id. at 106.

that Mr. Lewallen orally identified to him which mass spectrum to use from that sheet. Record Ex. 21, at 101. In a letter to Baylor dated July 14, 1993, Dr. Angelides argued that Mr. Lewallen had taken Dr. Jones's mass spectrum "which he knowingly claimed as his own at a time shortly before I dismissed him from my laboratory" and then included it in "a folder he compiled and presented to me along with some of his original data and work on the disulfides." Record Ex. 37, at 2; Record Ex. 36, at 2; see also Record Ex. 39. Dr. Angelides took the position that Mr. Lewallen's motive in misusing other researcher's data was laziness and desperation to remain in the graduate program. Record. Ex. 37, at 2. However, Dr. Angelides did not explain why such motives would cause Mr. Lewallen to include others' data in a folder that Dr. Angelides claimed Mr. Lewallen compiled as Mr. Lewallen was leaving the laboratory anyway.

Mr. Lewallen's testimony about this folder, before the Panel and during the Baylor investigation, directly contradicted Dr. Angelides's. Thus, Mr. Lewallen stated --

> Yes, it [the sheet of four mass spectra] was contained within a folder labeled by Dr. Angelides and was within a collection of isolated sheets, some photocopies of materials that I had prepared and some pages of Dr. Angelides' handwritten notes on the snail toxins, peptides for biosynthesis, and so forth. This manila folder was not a part of my own experimental notebooks. I believe it was a folder compiled by Dr. Angelides, not by me. I had never seen this page of four spectra (II.C.1.4) before the investigation committee showed it to me.

Lewallen WD at 24; see also Baylor Report at 64-65.

The Panel weighed the conflicting accounts of Dr. Angelides and Mr. Lewallen about the source of the mass spectrum used in Figure 2B and concluded that Mr. Lewallen's account was more credible for the following reasons. First, had Mr. Lewallen, as Dr. Angelides alleged, presented another laboratory member's work as his own in an effort to misappropriate it, it appeared to the Panel unlikely that Mr. Lewallen would then leave the raw data (along with other mass spectra of Dr. Jones, still bearing the other scientist's name) in a folder that he compiled for Dr. Angelides on his departure. Second, Dr. Angelides had possession and control of and the most ready access to both Mr. Lewallen's records and Dr. Jones's data. See Jones WD at 12. Third, the folder was marked in Dr. Angelides's handwriting, contained data from sources other than Mr. Lewallen (including Dr. Angelides and Dr. Jones), and had no demonstrable connection with Mr. Lewallen's research notes other than Dr. Angelides's own claim that it belonged with them. See Lewallen WD at 24. Fourth, Mr. Lewallen testified, with much corroboration discussed above, that he did not obtain useable mass spectra results, and, further, that as a consequence, he had no mass spectra at all in his data records. Tr. at 2092; Lewallen WD at 6, 23. Dr. Angelides did not identify any other mass spectra in any of Mr. Lewallen's records other than this contested sheet. The Panel concluded that the absence of any other mass spectra in his records further corroborated Mr. Lewallen's account that he never obtained meaningful results from any of the

samples that he submitted for analysis.[24] Fifth, Dr. Angelides did not produce any evidence that Mr. Lewallen ever prepared a figure or label for this mass spectrum, claiming that Mr. Lewallen simply gave him the sheet of four mass spectra and orally claimed that this one was what Dr. Angelides described it as in the grant application.

The Panel concluded that Dr. Angelides was solely responsible for the presentation of the HPLC profile and the mass spectrometry data in the GM48816-01 grant application.

3. Intentionality of false presentation of these HPLC and mass spectrometry data

The next question to be considered is whether Dr. Angelides was aware that the HPLC and mass spectrometry were not, in fact, what he described them as being in his grant application. The Panel concluded that he was aware of the true nature of these data and that he intentionally presented them falsely. We address first the reasons that we concluded that he knew that the HPLC was not a representative and typical profile of CNBr-digested sodium channel and then the reasons that we concluded that he knew the mass spectrum was not of a sodium channel peptide resulting from CNBr-digestion.

As mentioned above, Mr. Lewallen testified that he showed the composite profile to Dr. Angelides in order to illustrate the difficulty he was encountering in obtaining reproducible tracings even from a single sample. He testified further that, when he did so, he specifically explained to Dr. Angelides that the profile was produced by combining two different tracings. Tr. at 1165. This testimony suggested that Dr. Angelides was aware of the true nature of this profile before presenting it in his grant applications.

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[24]Dr. Angelides's argument that entries merely showing submission by Mr. Lewallen of peptides for mass spectral analysis cast doubt on the absence of mass spectra in his surviving records is not persuasive in the face of the weight of the testimonial evidence. See Ang. Br. at 41-42. Further, as Dr. Angelides acknowledged, most of the entries appeared to be control samples. Id. Dr. Angelides also challenged Mr. Lewallen's claim to have had no mass spectra by citing to testimony by Dr. Jones to demonstrate that Dr. Jones once claimed to have been shown a mass spectral analysis by Mr. Lewallen. Ang. Br. at 41. Dr. Angelides did not offer for the record the actual prior statement of Dr. Jones on which he relied. In his response to Baylor, Dr. Angelides quoted a brief excerpt allegedly drawn from Dr. Jones's testimony before Baylor in which Dr. Jones says he is "pretty sure" Mr. Lewallen showed mass spectral data to the laboratory, or that if Mr. Lewallen did show it to the laboratory, he would surely have shown it to Dr. Jones because they were "very close." Ang. Resp. to Baylor Report at 27. This out-of-context, unauthenticated, and extremely vague excerpt does not suffice to contradict the testimony of numerous witnesses before us, including Dr. Jones himself, to the effect that Mr. Lewallen obtained no useful mass spectral data in this project. See Jones WD at 9.

Dr. Angelides stated in his brief that he recognized that the HPLC profile presented in his grant represented a composite of two tracings as early as July 1992.[25] Ang. Br. at 35. However, he also contended that, even looking at it today, he could reasonably interpret the profile as a complex pattern that could have been generated by either trypsin- or CNBr-digested sodium channel with a baseline. Id. A visual inspection of the profile clearly demonstrates to the independent observer that it contains two apparent baselines and two tracings with different peaks. Dr. Angelides did not produce from the many HPLC tracings which both parties agreed were contained within Mr. Lewallen's records any other HPLC tracing which resembled this composite. Given this fact, as well as the testimony reviewed above about the widespread awareness in the laboratory about Mr. Lewallen's frustration with the results he was obtaining from the HPLC machine, it was not credible that Dr. Angelides could reasonably have believed this profile to have been "representative and typical" of either a trypsin- or CNBr-digested sodium channel.

In any case, Dr. Angelides conceded that the profile could not represent both trypsin- and CNBr-digested samples. Tr. at 1500. Yet, he presented the same profile in different grants making these incompatible claims. This change was significant because the GM48816-01 specifically pointed to the laboratory's new development of a "more sensitive detection and chemical characterization method" to identify disulfide-linked peptides using CNBr cleavage. Record Ex. 13, at 14. Thus, Dr. Angelides had a reason to alter the identification of the HPLC to appear to illustrate the most recent development that he was claiming for this project. The Panel found it highly unlikely that this repeated and self-serving use of the same, very distinctive composite HPLC profile could have occurred by accident.

Turning to the mass spectrum, substantial evidence in the record suggests that Dr. Angelides not only had possession of these data but had reason to know their true provenance. Dr. Jones had left Dr. Angelides's laboratory in February 1991 and had turned his data and records over to Dr. Angelides. Therefore, Dr. Angelides had ready access to Dr. Jones's data. In addition, Dr. Angelides, unlike Mr. Lewallen, was actively involved in reviewing Dr. Jones's work and hence would have had reason to be familiar with the data Dr. Jones had produced. Further, on the face of the mass spectrum itself, several features indicated that this analysis was not produced from Mr. Lewallen's samples from the HPLC shown in Figure 2A. As noted, Dr. Jones's name appeared on the mass spectrum itself. Also, the mass spectrum is dated October 19, 1990 while the HPLC tracing is dated May 17, 1989. Dr. Jones testified: "We would never wait a year and a half after the HPLC" to run the mass spectrum analysis. Jones WD at 11. Dr. Angelides argued that it was possible to store peptide samples for later testing and suggested that Dr. Jones might have done so with some of his samples. Ang. Br. at 12-13, 46-48. However, even if the disparity

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[25]In earlier testimony before the Baylor Sub-Committee on September 9, 1993, Dr. Angelides asserted that he discovered that the HPLC was a composite only on reviewing data in February 1993. Record Ex. 17, at 130-32. Thus, he testified: "I certainly didn't recognize it in 1989 and I didn't recognize it in 1992, that it was a composite. I only recognized it in 1993." Id. at 131.

in dates and names did not make it impossible for the mass spectrum to represent Mr. Lewallen's sample, those features certainly raise questions about why Dr. Angelides would accept the data as such without inquiring further.

Even more important, however, is the compelling evidence that Dr. Angelides had direct knowledge of this specific mass spectrum because he himself had planned the inclusion of these data in a draft manuscript he was coauthoring on the conantokin-G project during the summer and fall of 1991. The other authors were Dr. Jones, Dr. Benke, and Dr. Collingridge. On August 5, 1991, Dr. Angelides sent an early draft of the proposed paper (with a handwritten cover note) by facsimile transmission to Dr. Jones requesting his assistance in revising it for submission to Science. ORI Ex. 38, at 1. This draft contained a handwritten sketch by Dr. Angelides to show where the mass spectrum should be inserted and had attached to it the same mass spectrum that appeared as Figure 2B in the GM48816-01 grant. ORI Ex. 38, at 1, 24, 26; Benke WD at 5. Dr. Angelides acknowledged having sent this draft to Dr. Jones. Tr. at 1691-97.

Dr. Benke, who wrote the first draft of the paper, testified that Dr. Angelides was well aware of the contents of the proposed paper and had numerous conversations with him about it, including discussions specifically about Dr. Jones's data. Benke WD at 4, 6. Dr. Benke testified that he was certain that Dr. Angelides knew that this mass spectrum was generated by Dr. Jones using conantokin-G peptide. Tr. at 1099; Benke WD at 6. Dr. Jones said that Dr. Angelides "definitely was familiar with this data as we discussed it on numerous occasions." Jones WD at 11. Dr. Collingridge confirmed that all the authors discussed all the figures. Collingridge WD at 5-9.[26] In the face of the uniform testimony of the co-authors about Dr. Angelides's active involvement and familiarity with these specific data, Dr. Angelides's argument that the draft manuscript did "NOT contain the mass spectrum as claimed by ORI and furthermore there was no evidence or testimony that Angelides had ever seen this manuscript or that data contained therein" is untenable. Ang. Br. at 44 (emphasis in original).[27]

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[26]In questioning Dr. Collingridge, counsel for Dr. Angelides indicated that ORI took the position that Dr. Angelides "constructed and removed figures without consultation with any of the co-authors." Collingridge WD at 8. There is no evidence that ORI took this position, and Dr. Collingridge denied that this occurred in regard to the paper from which the mass spectrum was removed before publication. Id. The significant point for the Panel is that Dr. Angelides was reported, even by his own witness, to have been in agreement with all the figures presented, and thus well aware of the contents of the drafts of the paper. Id. at 6-9.

[27]Dr. Angelides did not deny that the figure contained the same mass spectral data as that intended for the manuscript but argued he would not have necessarily recognized it because the heading information was not identical. Ang. Br. at 44. His position in this regard responded largely to language in the Baylor Report suggesting that the mass spectrum was removed from the manuscript and then used in the grant. Baylor Report at 69. However, Dr. Angelides denied that it was plausible for the manuscript version of the data to have been the source of the grant

(continued...)

The figure containing the mass spectrum at issue was removed from later drafts of the paper (prior to Dr. Angelides's submission of the GM48816-01 grant application). Dr. Angelides did not dispute that the figure was deleted but contended that Dr. Jones, not he, made this decision. Ang Br. at 44. The testimony on when and by whom the figure was deleted was not decisive. Dr. Benke testified that a meeting of the four authors was held at a 1991 Neurosciences convention and the decision was made among all the authors to exclude the mass spectrum from the manuscript. Benke WD at 7. Dr. Jones did not remember when the decision was made although he remembered that he was not pleased about it. Jones WD at 10. Dr. Angelides denied that he even attended the Neurosciences meeting in 1991. Ang. Br. at 46. He testified before Baylor that the mass spectrum was removed from the manuscript, along with two other figures, simply in order to meet space limitations for publication. Record Ex. 26, at 71. He denied that that incident would have caused him to recognize that he had seen this spectrum before when he later, as he asserted, received it for the grant in a different context. Id. at 68-70.

The Panel found that the testimony of the other co-authors made Dr. Angelides's position less credible. As summarized above, they testified that Dr. Angelides had not merely seen the same data in another context months before, but rather had himself pointed out where to place the mass spectrum in the manuscript, had engaged in active discussion about the handling of the figure, and, whether or not he personally excised it from the final draft, certainly had participated in and was aware of the decision to remove it. Drs. Benke and Jones were clear that Dr. Angelides would have recognized this mass spectrum. Furthermore, the time frames involved were very close -- the mass spectrum had to have been removed from the manuscript after August 1991 (if not at the November 1991 meeting), the grant was submitted in February 1992 and Dr. Angelides asserted that it was prepared before Mr. Lewallen left in September 1991. Certainly, Dr. Angelides's prior involvement with this precise mass spectrum makes it very implausible that Mr. Lewallen would have elected to take this particular one from Dr. Jones's records and present it to Dr. Angelides as his own in any effort to mislead Dr. Angelides.

Finally, Dr. Angelides had a motive to intentionally falsify these figures in the GM48816-01 grant application. He offered no other data to substantiate the claims he had made about the

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[27](...continued)
figure because the format of the header information shown on the two matching mass spectra differs -- the grant figure has three lines of identifying information (as does the presentation of this same mass spectrum in the sheet of four mass spectra in the Disulfide Bridges folder discussed earlier), while, in the manuscript version, the top-most line of information does not appear. Compare Record Ex. 1, at Enc. II.C.1.4 with ORI Ex. 38, at 26. The significance of Dr. Angelides's removal of the mass spectrum from the manuscript was not to show that he took the precise presentation of the data and inserted in the grant. Rather, it is that his use of this specific mass spectrum (however labeled) to falsely represent a sodium channel peptide, under circumstances where his attention was so recently drawn to the data so that he should have been aware of its true identity, was evidence of intentional falsification.

location of disulfide bridges. Mr. Lewallen testified that the figures significantly enhanced the perceived progress. Thus, he testified that he --

> was shocked to actually see what [Dr. Angelides] claimed about the disulfide bridges project in the grant applications that we just reviewed. The grants claim success in identifying disulfide bridges, which was the major thrust of my work in the lab and an important goal in the biochemical characterization of the sodium channel protein in the grant applications. The false statements regarding my work increase throughout the grant applications until in the GM48816-01 grant he actually shows HPLC and mass spec data for the sodium channel. This would have been a significant accomplishment. It would have demonstrated success in most of the work I was attempting. If I had obtained such data, I seriously doubt that Dr. Angelides would have dismissed me from the lab, and I certainly would have been presenting the data to my advisory committee. Dr. Angelides and most people in the lab knew I had never identified even one disulfide bridge. He knew I had not obtained reproducible HPLC profiles, and never obtained a good mass spectrum. He simply falsified all these results.

Lewallen WD at 25-26. One of his thesis committee members confirmed that he repeatedly told them that he had no success and thus no data to present. Tr. at 262-63 (Hamilton).

Dr. Angelides argued that he had no reason to present a false mass spectrum because no reviewer comments suggested that he should present a mass spectrum and no evidence established that its inclusion would have influenced funding of the grant "on its own." Ang. Br. at 48. Dr. Angelides presented no testimony to support the premise that only data directly responding to a reviewer's comment or data sufficient per se to determine the funding decision are material to an application submitted to solicit funds. Nothing in the record contradicted the evidence of the application itself that presented these figures as demonstrative of accomplishments in the disulfide bridges project. Unquestionably, had they been accurately identified, the grant was less likely to be funded.

4. Additional arguments of Dr. Angelides relating to these HPLC and mass spectrometry data

Dr. Angelides claimed in his post-hearing brief that neither the HPLC tracing nor any reference to it was actually in the NS24606-05 Deferral. Ang. Br. at 37. The significance of this claim, even though no independent charge of scientific misconduct was made in relation to the HPLC tracing in the deferral submission, was that Dr. Angelides argued that he prepared the GM48816-01 grant in 1991 (while Mr. Lewallen was still in the lab) almost directly from the deferral submission and had no reason at that time to consult his original NS24606-05 application (in which the same HPLC tracing admittedly did appear). Id. at 37-38. Hence, the implication was that he would not have been alerted to recognize that the HPLC he was submitting in the GM48816-01 grant was recycled and relabeled from the NS24606-05 submission three years

earlier. However, the HPLC appears as Appendix Figure 1 in the deferral grant submission which the parties offered as joint Record Exhibit R-11. If Dr. Angelides meant to imply (which he did not make clear in his briefing) that somehow only the textual response to the reasons for the study section's deferral should be treated as the deferral submission and that the appendix was not resubmitted or was not reviewed upon resubmission, he has provided no evidence to support this conclusion. The cover letter transmitting the deferral document to NIH stated that not only the response to the requests for additional information but also the Appendix (which included the HPLC as Figure 1) and letters of collaboration were forwarded. Record Ex. 11, at 1. In the textual response, substantive changes were made in the text of the discussion of planned and accomplished work on disulfide bridge determination. Compare Record Ex. 9, at 22-23, 28-29 with Record Ex. 11, at 4, 9-10. These revisions indicate that conscious attention was given to the disulfide bridge area in the effort to enhance the NS24606-05 grant application in response to the deferral action. Further, while the text no longer specifically cites Figure 1, the appendices had to have been reviewed and consciously included in the deferral submission because Dr. Angelides added data for Appendix Figure 3 which was not in the original NS24606-05 application. Therefore, the Panel rejected Dr. Angelides's assertion that the HPLC profile was not part of the deferral submission.

Dr. Angelides also argued that he could not be expected to tell merely from looking at the pattern of the mass spectrum used in Figure 2B that it was conantokin-G, especially as he is not an expert on mass spectrometry. Ang. Br. at 44-45. Therefore, he contended it was unreasonable to penalize him for not recognizing the error. There was some evidence to the contrary. Dr. Jones indicated in a letter he wrote to Baylor that he thought it unlikely that Mr. Lewallen could have confused this mass spectrum as one of his own on sodium channel peptide, since it was "considerably less complex than he might have expected." Record Ex. 43, at Att. II.2. However, even if Dr. Angelides would not necessarily have known the nature of the sample by recognizing the pattern of the data, that would not refute the overwhelming evidence that the data were sufficiently labeled to alert him that it was unlikely to be Mr. Lewallen's sample as claimed and that Dr. Angelides was well-acquainted with this specific mass spectrum.

Dr. Angelides contended in his defense that he voluntarily withdrew the GM48816-01 grant application in which these figures were presented from consideration for funding by NIH before the investigation resulting in the present charges arose. Record Ex. 15, at 16, 35; Record Ex. 28, at 2; Record Ex. 30, at Att. Dr. Elmer; Ang. Ex. 103. He claimed that he acted because of his own reservations about the data provided by Mr. Lewallen (and Dr. Wible) when his laboratory was unable to replicate their work after their departure. Id. Dr. Angelides later filed formal allegations of misconduct against Mr. Lewallen. See Record Ex. 29. His position thus was that he discovered the suspicious data himself and took all reasonable steps to respond to the questions raised, and therefore, should not be held responsible for them himself.

The facts do not support this account of events. Dr. Angelides wrote to NIH to withdraw the grant on July 30, 1992. See Record Ex. 30, at Att. Dr. Elmer. Although the inquiry leading to the present case did not begin until December 1992, earlier allegations were brought against Dr.

Angelides by Dr. Brown in the summer of 1992. See Baylor Report at 45. That inquiry ended without finding sufficient basis to proceed to an investigation and did not involve most of the charges concerning the grants and papers discussed in this decision. However, the GM48816-01 grant was withdrawn during the pendency of that inquiry. Therefore, the timing of the withdrawal is consistent with Dr. Angelides's having been conscious that this grant contained falsified data that might come to light if the inquiry resulted in a full investigation, rather than his simply becoming concerned on his own about the reliability of the results. This interpretation is bolstered by the fact that Dr. Angelides did not bring his charges against Mr. Lewallen and Dr. Wible until February 1993, when the charges in the present case had surfaced.

In addition, Dr. Angelides asserted that he himself identified the misrepresented mass spectrum to the Baylor Sub-Committee, which he was unlikely to do if it were a falsification. He also claimed that he was able to make the identification "only with Dr. Gaskell's help," apparently implying both that he would not have needed Dr. Gaskell's help if he already knew what it was or if its identity was obvious on its face. Record Ex. 30, at 5 (February 10, 1993 letter from Dr. Angelides to the Baylor Sub-Committee). However, Dr. Gaskell's December 21, 1992 letter to Dr. Angelides, on which Dr. Angelides relied, actually undercuts the implication that Dr. Angelides ever sought Dr. Gaskell's help in an independently-undertaken effort to identify this mass spectrum. Record Ex. 30 at Att. H. Rather, Dr. Gaskell informed Dr. Angelides of the "details of a request for information" received on December 11, 1992 from Dr. Arthur Brown (who first raised allegations against Dr. Angelides) relating to the data used as Figure 2A/B. Id. Dr. Gaskell told Dr. Angelides in the letter that he "recognized the data as derived from the collaborative program with you and Owen Jones; the mass spectrometric data were recorded by Ralph Orkiszewski in my laboratory." Id. He further reported that he had told Dr. Brown that he (Dr. Gaskell), Dr. Angelides, and Dr. Jones had "discussed the preparation of this work for publication" but that he did not know the current status of the draft paper. Id.

From this letter, it is clear that Dr. Brown, not Dr. Angelides, initiated the effort to identify the mass spectrum that purported to be digested sodium channel peptide. Further, the letter is a contemporaneous corroboration that Dr. Angelides had indeed been actively involved in the preparation of the manuscript including the mass spectrum. Finally, the fact that Dr. Gaskell was immediately able to recognize the mass spectrum shown to him out of context as relating to the conantokin-G project casts further doubt on the credibility of Dr. Angelides's position that he was not aware of the true identity of the data and merely relied on Mr. Lewallen who misrepresented them to him. Cf. Ang. Br. at 40.

The Panel concluded that none of the additional arguments offered by Dr. Angelides had any merit.

5. Conclusion on the presentation of these HPLC and mass spectrometry data

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for falsely presenting data in

Figures 2A and 2B of grant application GM48816-01. In each case, the Panel concluded based on the evidence before it that Dr. Angelides knew at the time that he filed the application that the data were not as he described them and that he intentionally misrepresented them.

D. <u>Overall Conclusion Regarding the Disulfide Bridges Project</u>

Based on the evidence before it and for the reasons described in detail above, the Panel thus concluded that Dr. Angelides intentionally made false claims about this project and presented falsified data in further support of those claims in an effort to improve the likelihood that his grant applications would receive funding from NIH. In reaching this conclusion, the Panel considered each and every argument advanced by Dr. Angelides and carefully examined all relevant evidence in the record (whether or not specifically mentioned in our discussion) to arrive separately at an evaluation of each charge relating to this project. The Panel found the evidence as to each of the charges addressed in this section sustained an independent finding of scientific misconduct. The Panel also made several overarching observations in regard to this project that further supported its conclusions. First, the long period of time over which the false claims were repeated and expanded and the multiple grant applications in which the data were falsified reduced any possibility that honest error or interpretation of data caused the misrepresentations. Second, the use of different types of false data to enhance the status of the project as a whole reinforced the conclusion that Dr. Angelides knowingly falsified the specific figures to further the impression of success.

Furthermore, the two alternative scenarios offered by Dr. Angelides, that Mr. Lewallen lied to him and gave him false data in a desperate bid to stay in the graduate program and that legitimate data once existed to support the textual claims but have suspiciously became unavailable, impressed the Panel as internally inconsistent, entirely without support in the record as a whole, and implausible in light of the context. It is unlikely that Mr. Lewallen would have given Dr. Angelides the composite HPLC profile and Dr. Jones's mass spectral analysis and misled him as to what they were, if he had at time quantities of data in the form of legitimate, successful HPLC profiles and mass spectra to show Dr. Angelides. It is unlikely that Mr. Lewallen would believe he could mislead Dr. Angelides with false data and claims of success while bemoaning his frustrating lack of success so widely. It is unlikely that Mr. Lewallen would offer false data and false claims for use in grant applications but then make no such claims to his thesis committee which would more directly decide his fate and would presumably be more easily misled than Dr. Angelides, not being themselves involved in the project. It is unlikely that Mr. Lewallen would leave among his records the clear evidence of his misuse of another's data, knowing that Dr. Angelides would have access to those records. It is, on the other hand, less implausible that Dr. Angelides would feel safe in retaining copies, since he had no reason to believe anyone else would access his records or have reason to review them.

Finally, Dr. Angelides's testimony about this project contradicted in many respects that of virtually all other witnesses, including other members of his laboratory. For example, Dr. Angelides alone seems to recall any successes being achieved or claimed in this project while

others uniformly remember him as angry and frustrated with consistent failure. Dr. Angelides is virtually alone in his recollection of always writing grants collaboratively and involving Mr. Lewallen specifically in the process. Similarly, the Panel found Dr. Angelides's assertions that Dr. Nutter had successfully accomplished work as an experimentalist that Dr. Nutter himself testified resulted in total failure shared a pattern with his attributions of success to Mr. Lewallen that Mr. Lewallen himself denied having achieved. Dr. Angelides's testimony about Mr. Lewallen's success in general conflicted with that of Dr. Hamilton from his thesis committee, and Dr. Angelides's testimony about Mr. Lewallen's mass spectrometry work conflicted with that of Dr. Gaskell from the mass spectrometry facility. Dr. Angelides's testimony about the mass spectrum in the draft manuscript conflicted with that of all the other co-authors; to believe Dr. Angelides would require us to reject the consistent testimony of his co-authors. Dr. Angelides also offered no reason why Drs. Benke, Hamilton, Gaskell, Nutter, and others would so consistently disagree with his account of events, if it were accurate.

II. Anti-peptide Antibodies Project

A. Introduction on the anti-peptide antibodies

In multiple grant applications between 1988 and 1992, Dr. Angelides reported work that his laboratory was conducting to develop antibodies to specific peptide sequences of the rat brain sodium channel. In total, Dr. Angelides described a battery of up to 26 different anti-peptide antibodies that had been developed, along with details of the sequences to which they corresponded in three sodium channel subtypes (RI, RII, and RIII). Twenty antibodies developed against synthetic peptides were listed in a table appended to several grants entitled "Sequence-Specific Antibodies Prepared by Principal Investigator," three more were described in later applications as having been prepared against new synthetic peptides, and three additional ones were described in another application as having been developed against peptides generated in yeast from cloned segments of sodium channel cDNA. The main experimentalist on this project was Mr. Lewallen, working at first along with Dr. Elmer (who left the laboratory in 1988).[28] Mr. Lewallen testified that the main goals of the project were as follows: "We hoped to raise antibodies that would detect all three sodium channel proteins, as well as raising antibodies that would distinguish between proteins created from the RI, RII and RIII genes, by reacting with only one of the three gene products. We also wanted to obtain antibodies against specific regions of the sodium channel. For these three aims, we selected sequences of (predicted) amino acids to which we planned on synthesizing peptides for use in immunizing rabbits." Lewallen WD at 26.

Dr. Angelides is alleged to have falsified claims about the existence of 15 such anti-peptide antibodies, in that Mr. Lewallen denied either having ever synthesized or injected the particular peptides involved. In addition, Dr. Angelides is alleged to have made false claims about the

[28]Dr. Angelides alleged that Dr. Wible was involved in obtaining channel fragments expressed in yeast, although she denied any such role. Tr. at 1580-82 (Angelides); Tr. at 2071-73 (Wible).

properties of those antibodies that did exist, in that only four of the antibodies showed any possible evidence of positive reactivity. During the Baylor investigation, Dr. Angelides's position was that Mr. Lewallen was the party who had to answer for the absence of data to support the claims made, and he lodged formal charges of scientific misconduct against Mr. Lewallen with NIH. See Record Ex. 29; see also Tr. at 1711 (Angelides). In the present proceeding, Dr. Angelides argued that his representations in the grants were "fully consistent with the results known in the laboratory" and that ORI overstated the utility or importance which Dr. Angelides claimed for the antibodies. Ang. R. Br. at 236. He asserted that ORI's charges were not well-founded because there were not enough data in the record to support the conclusions that certain antibodies did not exist or were not positive. Ang. Br. at 249. We therefore consider whether the statements and tables in the grant applications are consistent with the experimental results, based on the testimony and evidence before us. To the extent we find they are not consistent, we then consider whether Dr. Angelides or Mr. Lewallen was responsible for misrepresenting the existence or properties of these antibodies, and whether such misrepresentation was intentional.

In addition to the statements in the text, Dr. Angelides included Western blot data in one grant application submitted in October 1989, NS28072-01A1, Appendix Figure 2, that purported to illustrate the properties of six anti-peptide antibodies (three against synthetic peptides and three against peptides expressed in yeast). Record Ex. 8, at A-20. It is undisputed that the primary data from which the lanes shown in Figure 2 were derived did not come from experiments on anti-peptide antibodies. Ang. Br. at 299; Ang. R. Br. at 244. The original data were found in Dr. Elmer's records, identified as tests of monoclonal and polyclonal antibodies against the intact sodium channel. Dr. Angelides identified Mr. Lewallen as the experimentalist responsible for the data in Figure 2, but also identified Dr. Wible as having responsibility for the data described as involving antibodies against fragments expressed in yeast. Ang. R. Br. at 242-43; see also Ang. Notice of Appeal at ¶¶ 547 and 554, at 68. We therefore consider below who was responsible for the false identification of the data in Figure 2 and whether the misrepresentation was intentional.

B. Textual claims and table of anti-peptide antibodies

The earliest grant which contained challenged statements about the anti-peptide antibodies was NS24606-05, signed by Dr. Angelides on June 28, 1989. Record Ex. 9. The relevant text (with significant contested portions in bold text) is as follows:

> Preparation and Characterization of Polyclonal and Monoclonal anti-NaCh and Sequence-Specific Antibodies. **We have prepared a battery of sequence-specific antibodies** against the S4 region, amino- and carboxy-termini, and to putative transmembrane, extracellular, and intracellular regions using synthetic peptides to map NaCh topology and function. **These antibodies and their locations are given in Table I-Appendix**.

Id. at 24. Table I itself is titled **"Sequence Specific Antibodies Prepared by Principal Investigator**" and lists peptides "SP1 - 20," with a predicted sequence location, residue numbers, degree of conservation between NaCh I and II, and amino acid sequence listed for each. Id. at A-1.

In grant application NS28072-01A1, signed by Dr. Angelides on October 26, 1989, the following progress report included challenged statements (in bold) about work on this project:

> Preparation and Characterization of Polyclonal and Monoclonal Sequence-Specific Antibodies: In brain mRNA encodes at least three distinct NaChs subtypes (46); neither the molecular nor cellular relationships between these NaChs is known. While our polyclonal and monoclonal antibodies appear to have a selectivity for the 'neuronal' form of the NaCh we do not know whether this staining pattern corresponds to NaCh I, II, or III. In order to further dissect the cellular distribution of NaCh subtypes I, II, and III, **we have prepared several sequence-specific antisera** generated on the basis of differences in the primary structure of these NaChs. **Both anti-peptide antibodies and antisera obtained from proteins expressed in yeast from cDNAs encoding each of the NaCh I-III subtypes have been prepared**. While the anti-peptide antibodies show some selectivity on immunoblots, we have found that these antibodies typically have low titers, and in general we have been disappointed with their use and specificity for immunocytochemistry. However, **antibodies generated against NaCh-subtype fragments expressed in yeast as ubiquitin-fusion proteins (54) have produced high-titer subtype-specific antibodies. These antibodies have been very useful and specific in immunoblots, immunoprecipitations, and immunocytochemistry on cryostat sections** (APPENDIX, Figure 2, Panels A and B).[29] **With these antibodies we have now added subtype and sequence-specific antibodies to our NaCh antibody repertoire. These antibodies and their locations in the primary sequence are given in Table II - APPENDIX**.

Record Ex. 8, at 23-24. Table II in this grant had two parts, each labeled "**Sequence Specific Antibodies Prepared by Principal Investigator**." The first part listed the same peptides SP1-SP20 as shown in the table in the preceding grant, and the second part listed the fragments from cDNA expressed in yeast (NaCh I--461-493; NaCh II--459-492; and NACh III -- 1976-2009). Id. at A-22.

In the deferral response on grant application NS24606-05 Deferral, forwarded by Dr. Angelides on December 29, 1989, the text asserted that the laboratory had "**prepared several new peptides corresponding to IS7, residues 382-394 (SP21), IIS4, residues 801-818 (SP22), and IIIS6/IVS1, residues 1502-1517 (SP23) and have raised antibodies against these**

[29]As discussed in the next section, these data were alleged to be falsified.

peptides . . . ." Record Ex. 11, at 6. This submission also included the table of twenty sequence-specific antibodies. Id. at A-1.

Finally, the last grant application in which Dr. Angelides is charged with misrepresenting claims about anti-peptide antibodies is GM48816-01, dated January 31, 1992. Record Ex. 13. The text asserted that the laboratory had "**prepared a battery of sequence-specific antibodies against the IIS4 (residues 801-818/SP22), IS7 (residues 382-394/SP21), IIIS6/IVS1(residues 1502-1517/SP23) amino- and carboxy-termini, and using synthetic peptides**. These antibodies and their locations are given in Table I-Appendix." Id. at 15. Table I consisted of the same twenty sequence-specific antibodies "prepared by principal investigator." Id. at A-12.

Mr. Lewallen testified that he began the effort to develop anti-peptide antibodies in 1987-88 by synthesizing ten peptides (those listed in the grant tables as SP1-SP9, and SP12), conjugating and injecting five of them (those listed in the table as SP2-SP6), and then working with Dr. Elmer to test the resulting antibodies. Lewallen WD at 26-27. He asserted that, from this work, they obtained one possibly active antibody. Id. at 32-33, 38, 42-47. Dr. Elmer corroborated that he recalled Mr. Lewallen synthesizing approximately eight to twelve peptides while Dr. Elmer was in the laboratory, and that the result of that round of experiments was at most one antibody (identified by rabbit number as 7671) for which they obtained some reactivity on Western blots. Elmer WD at 78-81. Mr. Lewallen testified that, in 1990, after Dr. Elmer had left, he began a second round of injections using the peptides already synthesized to SP7-SP9 and SP12. Lewallen WD at 27, 32-33. From that round, he testified that he derived a second antibody that appeared to yield positive results. Id. Thus, he concluded that the project as a whole resulted in ten synthetic peptides, of which nine were injected into rabbits, giving "at best . . . two such antibodies that gave evidence of positive reaction." Id. at 33. He testified that he never got around to injecting SP1 or synthesizing SP10 and 11, and that he never even intended to make antibodies to the peptides listed as SP13-20 in the grant table, nor to SP21, SP22, or SP23 (which were added in later grants). Id. at 32-34, 42-43. Further, he testified that he never attempted to develop any antibodies to peptides from cDNAs expressed in yeast. Id. at 39-40.

ORI charged that Dr. Angelides falsified claims about the existence of antibodies corresponding to the peptide sequences listed as SP10-11, 13-20, 22, and 23, as well as the three antibodies to peptides claimed to have been expressed in yeast.[30] ORI further charged that even as late as

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[30]ORI did not make any charges relating to the antibodies corresponding to SP1 and SP21, although Mr. Lewallen testified that he did not inject SP1 into any rabbit and did not synthesize SP21. Lewallen WD at 46-47. ORI found the evidence on these antibodies equivocal. ORI Findings at ¶¶509, 515-517. The ambiguity in relation to SP1 largely arose from information from Dr. Pfenninger that he was given antibodies 7733 and 7676 (by rabbit numbers) to test. ORI considered that 7733 might be SP1, since the rabbit numbers for SP2 began at 7732. ORI Findings, ¶509; see also Tr. at 570-73 (Pfenninger); Hearing Ex. 7. However, evidence in the record clearly suggested that rabbit number 7733 was injected with the peptide corresponding

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1992 only four of the antibodies (those corresponding to SP1, SP3, SP5, and SP21) might have shown any indicia of positive reactivity on Western blots or immunoprecipitations. ORI Findings ¶517.

1. Primary data on the existence and properties of antipeptide antibodies

No data were produced by Dr. Angelides to document any of the claims in these grants about the existence or properties of the disputed antibodies. The Panel therefore reviewed the data and evidence that were in the record on the anti-peptide antibody project to determine whether in the aggregate it tended to support the testimony of Mr. Lewallen or Dr. Angelides.

The record includes four handwritten pages that Mr. Lewallen testified were part of his planning process with Dr. Angelides to decide which peptides to synthesize and inject, and preceded any injections of the peptides into rabbits. ORI Ex. 4; Lewallen WD at 32-33. The first page, which Mr. Lewallen identified as a "precursor" sheet, lists five peptides using a nomenclature that Mr. Lewallen testified he had developed based on the predicted position of the peptide and, sometimes, the sodium channel subtype, and then noting associated rabbit numbers, for example, peptide IC-C-TER and rabbit numbers 7730-34, 7670-71 or peptide IC-NaCh1 and rabbit numbers 7672-77. Lewallen WD at 31-32.[31] The succeeding pages include additional peptides

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[30](...continued)
to SP5. Hearing Exs. 38, 51. The ambiguity relating to SP21 largely arose from a letter from Dr. Eun-Hye Joe to the Baylor Sub-Committee in which she reported that she used an anti-peptide antibody called SP21 that was against residues 382-394 "or similar." Record Ex. 45, at Att. III.107. Mr. Lewallen suggested that the antibody called $SPII_1$ in Dr. Catterrall's naming convention (discussed later) was "similar" in location and might have been the one used. Lewallen WD at 43-45. In any case, Dr. Joe wrote that no written record of the experiments was retained because, after feasibility testing, the antibody was not used. Record Ex. 45, at Att. III.107. The Panel concluded that it was not necessary to resolve the ambiguities in relation to these two antibodies, since no charges were filed in relation to them. However, the Panel also concluded that the evidence presented by Dr. Angelides in relation to these antibodies did not undermine the credibility of Mr. Lewallen's testimony in relation to his work on this project.

[31]The original of Mr. Lewallen's list was included among Dr. Elmer's records with other materials relating to the anti-peptide antibody project, all of which, as discussed in the text, were consistent with Mr. Lewallen's testimony. Hearing Ex. 15. Mr. Lewallen also testified that ORI Exhibit 5 was an updated version of the same list with rabbit numbers added, and that he gave one or both versions to Dr. Angelides. Lewallen WD at 32. Dr. Angelides responded that these lists were undated and so did not in themselves establish that they constituted a "current or final count of those peptides and anti-sera" that Mr. Lewallen produced. Ang. Reply Br. at 239-40. Additional documents provided for the record showed efforts by Mr. Lewallen to highlight published peptide sequences as part of the planning process. See Hearing Ex. 33. However, the
(continued...)

similarly identified, plus three peptides identified by a different nomenclature (SPI and $SPII_{I}$ and $SPII_{II,}$) for a total of twelve peptides. Mr. Lewallen testified that the SPI and SPII names were from a 1987 paper in which Dr. William Catterrall reported successfully developing anti-peptide antibodies to these sequences. Lewallen WD at 32, 35-36; ORI Ex. 11B. For each of the twelve, the sheets provide information on amino acid sequence and the percentage of homology among sodium channel subtypes.

Mr. Lewallen's original records were not offered for the record by either party (although the box containing his materials was available to both parties at the hearing). ORI provided a summary of the antibodies for which data existed, and Mr. Lewallen adopted that table as accurate with minor amendments after reviewing both his own and Dr. Elmer's data, as well as the peptide synthesis logbook. ORI Ex. 9; Lewallen WD at 29-30; ORI Exs. 4, 5, 9; ORI Br. at 101; ORI Reply Br at 75.[32] Dr. Angelides did not produce contrary evidence as to the contents of Mr. Lewallen's records. The Panel therefore infers that Mr. Lewallen's extant records do support the summary of antibodies for which data show their existence or properties and that no extant records support the existence of the contested antibodies. Furthermore, Dr. Elmer's records were produced for the record and carefully reviewed by the Panel. See Hearing Exs. 14, 15, 51. They contained documentation of the first round of injections in 1987 consistent with the testimony of

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[31](...continued)
Panel found credible Mr. Lewallen's testimony that these documents were prepared as part of the planning process, in the course of selecting sequences for injection (and then identifying the ones that were synthesized and those that were injected). Dr. Angelides did not identify any evidence in these sheets or any later records showing that any of the contested antibodies claimed in the grants at issue here were ever produced.

[32]Mr. Lewallen testified as follows about the data which he reviewed and which were in the Baylor files made available at the hearing:

> I examined the records sequestered by Baylor. There were notes in my notebook of the antigen, the injection data and the rabbit numbers for the sera. I examined the synthesizer data sheets for the 10 peptides that I made, they provide my name, the sequence made (not present on the table), technical information relating to the reagent and syntheses, and the date of synthesis. Dr. Elmer kept records of the injection of the first set of rabbits, and I have seen calendar sheets for September and October 1987, where we recorded the dates and what was injected. For some of the rabbits the cage labels were retained, and I have seen copies of those from the files sequestered by Baylor. I had also prepared a handwritten summary of the antigen and the rabbit numbers that Dr. Angelides submitted to the Baylor Committee, and which I examined during the investigation. ORI Exhibit 5. Also, on the autorads or the photographs of Western blots, Dr. Elmer recorded both the rabbit number and the antigen name, and I saw those documents during the investigation.

Lewallen WD at 29-30.

Dr. Elmer and Mr. Lewallen. The Panel was able to trace the testing of the antibodies (by rabbit number). See id.; Hearing Ex. 38. In no case did the Panel locate a record of an anti-peptide antibody inconsistent with those that Dr. Elmer and Mr. Lewallen testified were produced and which were presented in the summary as amended by Mr. Lewallen.[33] ORI Ex. 9.

[33]Dr. Angelides argued that Mr. Lewallen's position about the existence of the contested anti-peptide antibodies had shifted since Mr. Lewallen testified before Baylor. Ang. Br. at 248, 269-72. The Panel did not find this argument persuasive. Dr. Angelides did not produce for the Panel the complete statements by Mr. Lewallen on which Dr. Angelides relied in making this argument, so we were unable to evaluate the claimed statements in context. From the excerpts that Dr. Angelides quoted, it is not evident that Mr. Lewallen's testimony was in direct conflict with his testimony before us. In addition, the witnesses called before the Baylor Sub-Committee did not have all of their records before them, as they did when testifying to this Panel.

2. Responsibility for and intentionality of textual claims and table of anti-peptide antibodies

Dr. Angelides indisputably wrote and signed as principal investigator each of the grants at issue here. Record Exs. 8, 9, 11, 13. In doing so, he undertook responsibility for the accuracy of the information in them. Dr. Angelides did not dispute, and ample testimony supported, the standard in the scientific community that a principal investigator may not report results in a grant application for which he lacks a good faith belief in the legitimacy and interpretation of the data. See Tr. at 1491, 1594, 1973 (Angelides); see also Tr. at 580 (Pfenninger); Berget WD at 8; Taylor WD at 7. This conclusion is in accord with prior rulings of the RIAP that, at a minimum, the "making of statements which are deliberately false or materially misleading about experimental results constitutes scientific misconduct," under prevailing standards in the scientific community even before the adoption of an explicit regulatory definition in 1989. See, e.g., Ruling in Sharma at 9-13 (May 10, 1993); Hiserodt at 17. However, Dr. Angelides argued that he did have a good faith belief in the accuracy of his claims because he necessarily relied on his laboratory workers and the data they showed him. We therefore consider whether Dr. Angelides demonstrated that he did rely in good faith on statements or data from Mr. Lewallen or Dr. Wible in making the claims and including the table of anti-peptide antibodies in the grants at issue.

Three possible scenarios are presented by the arguments of the parties on the contested synthetic peptide antibodies: (1) the contested antibodies never existed or never worked but Mr. Lewallen misled Dr. Angelides into believing they did; (2) the contested antibodies never existed or never worked, and Dr. Angelides knew it when he prepared the grants; or (3) the contested antibodies did once exist, and Dr. Angelides reviewed data supporting the claims made, but the records that would support their existence or their properties are lost or missing.

The Panel considered the likelihood of each of these scenarios in light of the record before it. We considered first the scenario under which Mr. Lewallen misled Dr. Angelides, and found it unlikely. On the face of it, for Mr. Lewallen to attempt to deceive Dr. Angelides about the development of so many antibodies would seem a very risky endeavor given Dr. Angelides's ready access at any time to all the original data, including records of protein synthesis and rabbit injections.[34] The challenged results claimed in the grants could not come from a single

[34]Dr. Angelides denied that he was suspicious of Mr. Lewallen, since suspicion was not a "personal characteristic" of his, and also asserted that he would have had no reason to check records to verify claims by Mr. Lewallen, because such an action would "break the fundamental trust Dr. Angelides placed in his laboratory personnel." Ang. Br. at 285. However, the point here is not whether Dr. Angelides did verify Mr. Lewallen's claims by checking laboratory notebooks and data, but rather that, were Mr. Lewallen planning to deceive, he would have been aware that, at any time, Dr. Angelides would have had the ability to undertake such a check. Mr. Lewallen would also have known that he would be called upon by Dr. Angelides to provide

(continued...)

experiment, from which Mr. Lewallen might have faked data to provide evidence of positive results. Peptide syntheses, conjugations, animal records, antisera injections, collection of sera, and testing of antibodies would logically have meant creation of a variety of records. See generally Ang. Br. at 259, n. 190; Lewallen WD at 29-30. Furthermore, Dr. Angelides agreed that he closely monitored Mr. Lewallen's work, in both weekly progress meetings and data reviews, and was well aware of the status of research in his laboratory. Ang. Br. at 275-76, 285; see also Tr. at 1135, 2087 (Lewallen). It is hence difficult to see how Mr. Lewallen could have sustained so large a deception about this project over several years without Dr. Angelides becoming aware of it (even after Mr. Lewallen's departure, since the last grant at issue was not submitted until 1992 and Mr. Lewallen left the laboratory in September 1991).

In addition, in Table I, every peptide on Mr. Lewallen's planning list was presented in the grants as yielding a functional antibody. Lewallen WD at 48. Such uniform success seems unlikely in a student whose otherwise frustrating lack of results was so widely remarked, and therefore makes it seem less plausible that he would have made such a claim to Dr. Angelides without supporting data or that Dr. Angelides would have uncritically accepted it.

Furthermore, the Panel received testimony that Mr. Lewallen was open about his difficulties with this project both with other members of the laboratory and with his thesis committee. Thus, Dr. Velazquez testified that "Mark never suggested to me or anyone else in my presence that he had . . . developed a battery of antipeptide antibodies. I do not believe he made any such representations to Dr. Angelides either." Velazquez WD at 4. Dr. Jones, who was in the laboratory from December 1987 to February 1991, reported that Mr. Lewallen discussed specific obstacles with him:

> Yes. Mark and I discussed a problem that we had with Dr. Angelides involving these antibodies. We both were concerned that if you are going to make an antibody against a synthetic peptide, then you have to make sure that the peptide is pure. Mark would tell me how he kept pushing Dr. Angelides to have amino acid analysis done on the peptides. Dr. Angelides wasn't interested in doing that and that bothered Mark. I think he was worried that the reason he wasn't able to get antipeptide antibodies in the first place was that the synthetic peptides he created were poor. I was fully aware that he was having problems making antibodies against these synthetic peptides. I did not really use any of the antisera, and I'm not sure if any were useful.

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[34](...continued)
antibodies to researchers in his own and Dr. Angelides's collaborators' laboratories.

Jones WD at 12-13.[35]

Dr. Hamilton testified that the thesis committee knew that Mr. Lewallen was trying to develop a battery of anti-peptide antibodies but that he never reported success in achieving that goal, which "would have been considered very good progress; not maybe as significant as mapping the disulfide bonds, but important to this." Tr. at 272. Her recollection is corroborated by Mr. Lewallen's progress report of January 10, 1991 to his thesis committee, in which he wrote --

> I synthesized four peptides derived from the amino acid sequence of the sodium channel from rat brain, three corresponding to peptides which had successfully produced antibodies in William Catterall's laboratory, the fourth derived from sodium channel III deduced in Rolf Joho's lab. . . . Harvested antisera was examined for antibodies by detection on Western blots, dot blots and an immunoprecipitation assay. Of the eight rabbits initially injected, two died during the production of antibodies due to complications with the anaesthesia. The remaining six rabbits yielded one antibody which was positive on both Western blots and in the immunoprecipitation assay.

Record Ex. 45, Att. III.115, at A-211. This progress report is consistent with the available records reviewed by the Panel as to the results of the 1990 round of antibody production.[36] Submitting this report would make little sense if Mr. Lewallen had led Dr. Angelides, and the rest of his thesis committee, to believe that a full set of 20 functional anti-peptide antibodies had been obtained as early as June 1989, and 26 by the end of that year, as claimed in the grant applications. Dr. Angelides signed the progress report in 1991. Yet, he repeated the claims of having successfully developed a battery of anti-peptide antibodies the following year, even after having dismissed Mr. Lewallen from his laboratory. See Record Ex. 13, at 15.

Furthermore, the Panel concluded that the credibility of Mr. Lewallen's testimony about the anti-peptide antibody project was enhanced by the independent corroboration by Dr. Elmer of the portions of the project that occurred during Dr. Elmer's tenure in the laboratory, as well as by the consistency of Dr. Elmer's records with the testimony of both Dr. Elmer and Mr. Lewallen.

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[35]Dr. Angelides asserted that Dr. Jones testified in an earlier proceeding that Mr. Lewallen successfully obtained a battery of anti-peptide antibodies. Ang. Br. at 271-72. However, the testimony which Dr. Angelides cites merely reported Dr. Jones's awareness that Mr. Lewallen synthesized peptides and tested antibodies and concluded that "a few probably . . . worked okay." Id. This does not contradict the testimony of Mr. Lewallen or Dr. Jones's testimony before the Panel that the project did not result in a battery of functional antibodies.

[36]For example, SP7-9 corresponded to peptides reported by Dr. Catterrall and SP12 corresponded to RIII from Dr. Joho, and SP7-9 and SP12 are the four peptides that Mr. Lewallen testified he injected in the second round. See ORI Ex. 11; Lewallen WD 32-33, 45.

Turning to the scenario in which Dr. Angelides knowingly claimed to have functional antibodies which did not in fact exist, the Panel noted that Dr. Angelides, unlike Mr. Lewallen, wrote for an audience that had no way of knowing or checking if the reported antibodies represented positive results for all of the peptides attempted, and therefore would not necessarily have been suspicious of the perfect success rate. Also, Dr. Angelides, unlike Mr. Lewallen, could take steps to avoid access to his grants by those who would be likely to know the facts about the status of the research. Finally, Dr. Angelides, unlike Mr. Lewallen, could reasonably assume that the grant reviewers would have no opportunity or occasion to access the raw data and records to double check his assertions. Reviewers were not able to request any of the antibodies, since knowledge of their existence was privileged. The Panel therefore concluded that, if no data really existed to document the disputed claims, it was far more likely that Dr. Angelides knew it than that Mr. Lewallen misled him.

As to the likelihood that data did support the claims at the time they were made but were now unavailable, the Panel found this scenario implausible and unsubstantiated by any independent testimony or documentation. All of the witnesses other than Dr. Angelides likely to have knowledge of the contents of the records before the Baylor investigation denied that such data ever existed. See, e.g., Lewallen WD at 47-48; Elmer WD at 79. Dr. Angelides offered no specific description about what data were missing from the existing records that he had previously reviewed. He claimed in his argument that Mr. Lewallen's existing notebook records showed that immunoblots and immunoprecipitations were done with anti-peptide antibodies, some of which might have been positive. Ang. Br. at 248, 277; Ang. R. Br. at 236-38. [37] However, although Mr. Lewallen's materials were available at the hearing, Dr. Angelides failed to offer the notebooks into evidence, and expressly declined to do so when the Panel offered him an additional opportunity after the hearing. Ruling on Outstanding Motions at 6 (Oct. 26, 1998). Further, he did not specify which anti-peptide antibodies were allegedly referred to in the notebooks as having been tested or as having yielded positive results on tests. There was thus no

[37]Dr. Angelides's position was that it was unfair that "[d]espite the fact that such data was available in Mr. Lewallen's records, supported by his notebook entries for the variety of tests that he employed to characterize the antibodies, [Baylor] and ORI now shift the burden on Dr. Angelides to produce those records." Ang. R. Br. at 238-39. Thus, Dr. Angelides argued that ORI did not have enough data to justify its (and its experts') assertions about what peptides were synthesized, what antibodies existed, and how well they worked. This position turns logic on its head because it ignores the experimentalist's testimony that no data existed and suggests that Dr. Angelides had no responsibility to present the basis for the claims he put forth in his grant applications (when they were questioned).

basis to conclude from any alleged notebook references that data ever existed to support the claims about the contested antibodies.[38]

Further, Dr. Angelides offered no plausible explanation of how data relating only to the challenged antibodies could have been excised from the records while leaving intact data about the uncontested peptides and resulting antibodies which were being synthesized, injected, collected, and tested during the same rounds of experiment. In addition, he presented no testimony, other than innuendo in his own argument, tending to show any such tampering with the documentation of the anti-peptide antibodies. Despite having several members of the Baylor Sub-Committee present as witnesses at the hearing, Dr. Angelides did not cross-examine any of them as to the handling of any records relating to the anti-peptide antibodies.

The Panel concluded that the claimed existence and properties of the contested antibodies to synthetic peptides were not supported by any documentation. The Panel also concluded that a preponderance of the evidence demonstrated that Dr. Angelides knew that to be the case at the time he inserted each of the highlighted claims in the text of his grant applications.

Turning to the list of 20 antibodies included as an appendix table in multiple grant applications, Dr. Angelides at times took the position that Mr. Lewallen prepared the table either himself or with secretarial help, made corrections to it, and provided it to Dr. Angelides who relied on it, and at other times that Mr. Lewallen was given the table by Dr. Angelides and asked to make corrections. Tr. at 1573-74 (Angelides); Ang. Br. at 278. As evidence that Mr. Lewallen was responsible in either case as the source of the information presented in the table, Dr. Angelides argued that a copy was found among Mr. Lewallen's records, and that Mr. Lewallen acknowledged reviewing the table and making handwritten corrections on the table. Ang. Br. at 278-84; Tr. at 1573-74 (Angelides). Nevertheless, Dr. Angelides denied that he ever stated that Mr. Lewallen "deceived" him with regard to the table. Ang. R. Br. at 240-42.

Mr. Lewallen testified that Dr. Angelides gave him a draft version of this table and asked him to check the accuracy of the amino acid sequences. Lewallen WD at 33, 36-37. He testified, however, that the draft version did not contain the heading "Sequence Specific Antibodies Prepared by Principal Investigator." Id. at 37-38. It was not disputed that a version without the heading as described was found in Mr. Lewallen's records during the Baylor investigation. ORI

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[38]The only extant piece of data of Mr. Lewallen's to which Dr. Angelides pointed in the record was a dot blot, but no testimony was offered interpreting this dot blot and nothing on the face of the dot blot evidences that it relates to any of the contested antibodies. Cf. Ang. Br. at 277; Ang. Ex. 17. Dr. Angelides also cited to a Western blot, but that was data of Dr. Elmer's, and was clearly labeled as testing polyclonal and monoclonal antibodies to the intact sodium channel. Ang. Br. at 277; Ang. Ex. 1.

Ex. 6; ORI Br. at 102; Ang. R. Br. at 240.[39] Mr. Lewallen did not dispute that he made handwritten corrections to the information on the table as was requested of him.[40] Lewallen WD at 33. Mr. Lewallen testified that, at the time, he was not aware that the table was intended to claim that these antibodies had already been prepared, as opposed to serving as a proposal of peptides to be synthesized and injected in the future. Id. at 38-39. He further testified that he was not aware that the table would be or had been used in any grant application and that he was never asked to review any grant application in which it appeared. Id. Further, Mr. Lewallen asserted that the SP designations assigned to the peptides in the table were not those which he used for the peptides and were instead assigned by Dr. Angelides himself. Id. at 48; see ORI Exs. 4, 5. This testimony was corroborated by Dr. Elmer who stated that Mr. Lewallen used the nomenclature based on the intracellular or extracellular location of the peptide. Elmer WD at 80.[41] Dr. Elmer testified that he was "not aware of any use of the 'SP' designation by Mark

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[39]Dr. Angelides claimed that a version with Mr. Lewallen's corrections that did contain the heading was also found in Mr. Lewallen's records, but this claim was not supported by the record. Such a sheet does exist, but the notations match those on the sheet without the heading. Compare ORI Ex. 6 with Record Ex. 45, at Att. III.103, at A-127. It is impossible to tell whether the heading was added after the corrections were already on the page. Further, testimony before the Baylor Sub-Committee suggested that this version of Table I was obtained from Dr. Angelides's records, not Mr. Lewallen's. See Record Ex. 21, at 172. Dr. Berget stated that, leaving aside the uncorrected version used in the grant, two versions of the table with the corrections noted existed: one "that came from Mr. Lewallen's primary data that is lacking a title at the top of the page" and one "that contains the title at the top of the page as provided by Dr. Angelides." Id. Dr. Angelides did not dispute at the time that the second version came from his own records but only asked why Mr. Lewallen made corrections to the table (with or without the heading) if he had not made these peptides. Id. at 172-73. As noted in the text, the explanation to which Mr. Lewallen testified, and which the Panel found credible, was that he understood this table to plan the sequences to which antibodies might be developed, not to report those already made.

[40]In his initial testimony before Baylor, Mr. Lewallen did not recognize the notations as his own, but in a later appearance he stated that he did make corrections to the peptide sequences. Record Ex. 21, at 170-71.

[41]Dr. Angelides questioned the credibility of Mr. Lewallen's claim not to have used the SP naming system by pointing to an excerpt from a published paper containing sodium channel sequence information on which Mr. Lewallen had made handwritten notations showing regions to which he planned to make peptides. See Ang. Br. at 278; ORI Ex. 10; Hearing Exs. 32 and 33. The notations include SP1, $SPII_I$ and $SPII_{II}$, at locations corresponding to those for which Dr. Catterall had assigned those designations. See ORI Ex. 11B. Dr. Angelides pointed, however, to the fact that Mr. Lewallen had written in the names SP19 and SP20 for other peptides as evidence that Mr. Lewallen did use that nomenclature. Ang. Reply Br. at 240-41; Tr. at 1571-73

(continued...)

[Lewallen] to identify the peptides or the anti-peptide antibodies that he was working with in Dr. Angelides' laboratory" and that he himself used "rabbit numbers and Mark's antigen names" in recording notes and data, and not any SP designations. Id.; see Record Ex. I, at Enc. II.C.4.42. The Panel concluded that Dr. Angelides, not Mr. Lewallen, was responsible for the preparation of the table as presented in the grant applications.

Next, we turn to the anti-peptide antibodies reported in NS28072-01A1 as having been generated against protein fragments expressed by cDNAs in yeast. Record Ex. 8, at 24. Here, we discuss the source and accuracy of the textual claims that these antibodies had been obtained and had demonstrated high titer and specificity in various immunological assays; in the following section, we address the allegedly falsified Western blot data presented to support these claims. Dr. Angelides attributed the information presented in regard to these antibodies variously to Mr. Lewallen and Dr. Wible. Tr. at 1580-82 (Angelides). Thus, Dr. Angelides testified: "The peptide/anti-peptide, as I had indicated, antibodies were done by Mr. Lewallen. Those antibodies that were prepared from cDNAs expression which required molecular biology were those by Dr. Wible. . . . I had seen during the course of Dr. Wible's work using a system which was a system, a yeast expression system. I had seen fragments that she had prepared on gels and that she had subsequently injected into rabbits. I had seen the Western blots in comparison to our standard at the time, which was the antibody 7493. This is what she had presented to me during the course of these experiments." Tr. at 1580-81. In his answer to ORI's charges, Dr. Angelides wrote that Mr. Lewallen was "the source of information and data on anti-peptide antibodies" and "had ready access to data in the laboratory." Ang. Resp. to Charge Letter, at ¶¶547, 554. Given Dr. Angelides's vacillation in attributing responsibility to Dr. Wible and Mr. Lewallen for the

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[41](...continued)
(Angelides). If anything, these exhibits support the opposite conclusion. As Mr. Lewallen testified, the SP19 and SP20 notations are from other published papers by Dr. Catterall, and their locations do not correspond to the sequences assigned those numbers by Dr. Angelides in the appendix table. Lewallen WD at 35-36; ORI Ex. 11. Instead, those locations correspond to SP13 and SP14 in Dr. Angelides's naming system. Dr. Angelides also suggested that Mr. Lewallen was inconsistent in that he previously acknowledged using the SP nomenclature during the Baylor investigation, but the references cited by Dr. Angelides all demonstrate that Mr. Lewallen consistently explained that he used only those SP numbers assigned by Dr. Catterrall to a few of the peptides he worked with (which did not correlate with those SP numbers assigned by Dr. Angelides). Cf. Ang. Br. at 278-83; see, e.g., Record Ex. 21, at 165-66. The Panel found credible Mr. Lewallen's testimony that he would never have given the same peptide two different SP designations, because it would generate unnecessary confusion, and that he was well aware of the peptides used by Dr. Catterrall, so that it was unlikely it was he who selected the SP nomenclature used in the grant tables. See Lewallen WD at 35-36. In addition, in reviewing the data on testing of the anti-peptide antibodies in Dr. Elmer's records, the Panel found that Mr. Lewallen's nomenclature or rabbit numbers (rather than the SP designations in Dr. Angelides's tables) were consistently employed, further corroborating Mr. Lewallen.

preparation of and reporting on these antibodies, the Panel considered the evidence as to each of them.

Dr. Wible denied forcefully that she ever worked in yeast at all during the time she was in Dr. Angelides's laboratory and testified that she never attempted to express such peptides. Tr. at 2071-73. She testified that she was "certain of that, because when I moved to Cleveland in 1995, I started working with yeast, and everything was new to me -- completely new." Tr. at 207-72. Further, she testified that she never injected rabbits to create an antibody or told Dr. Angelides that she had. Id. at 2072. Dr. Wible's notebook dated September to December 1989 is in the record (Hearing Ex. 6) and all of her laboratory notebooks confiscated by Baylor were made available to Dr. Angelides for review. Yet, Dr. Angelides did not identify any specific entries or data of Dr. Wible's that would demonstrate any efforts, much less successful results, in the claimed project, nor was the Panel able to locate any in its independent review of the notebooks it had.

Mr. Lewallen also denied that the claims about these antibodies resulted from any work that he had done in the laboratory or any information that he provided to Dr. Angelides. Lewallen WD at 39-40, 46-47. Furthermore, Mr. Lewallen testified that he was not aware of anyone in the laboratory producing fragments of sodium channel in a yeast system and using them to produce antibodies, and that he believed he would have been aware of any such work in the laboratory. Id. at 41. Again, Dr. Angelides presented no data or notebook records to the contrary nor did the Panel locate any.

The record as to these anti-peptide antibodies is particularly clear because no evidence whatsoever was presented, other than the testimony of Dr. Angelides, that a single fragment was ever expressed in yeast or injected into a rabbit. Unlike the antibodies to the synthetic peptides, some of which were admittedly made and tested, in this area it is not necessary to distinguish the amount of work done on each fragment. Consequently, even less potential arises for confusion or honest error in the reporting on these antibodies. In the absence of any evidence to support the production of any antibodies to any fragments, it clearly cannot be substantiated, as one grant claimed, that they were "very useful and specific in immunoblots, immunoprecipitations, and immunocytochemistry," and, in fact, no data were offered by Dr. Angelides to support that claim.[42] Record Ex. 8, at 24. Further, Dr. Angelides offered no evidence of these "very useful" reagents being used in any experiments. The Panel concluded that the claims made about the antibodies to sodium channel fragments expressed in yeast were false, that Dr. Angelides was responsible for including these claims in the text of the grant, and that he did so intentionally, knowing that they were false.

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[42]The grant referred to Figure 2 in support of the claim, but Dr. Angelides conceded that the data presented there on these antibodies were from an unrelated experiment of Dr. Elmer's, and Dr. Angelides did not present any alternative data to the Panel to support the substantive claims made in the text.

The Panel further concluded that Dr. Angelides had substantial motivation to overstate the success of his efforts to obtain a battery of anti-peptide antibodies. Had Dr. Angelides accurately reported that he had at most four (or perhaps only two) functional anti-peptide antibodies, instead of 20-26 anti-peptide antibodies as claimed in the grant applications, it would have been evident to reviewers that his work on this project was significantly less advanced. Notably, only the application that made the most expansive claims about the number of and utility of the anti-peptide antibodies and that included Western blot data purporting to substantiate those claims received funding. See Record Ex. 8, at 23-24, App. Figure 2. A competing laboratory had already produced and reported in publications on the characteristics of a number of functional peptide-specific antibodies to the rat brain sodium channel in publications in 1987, 1988, and 1989. ORI Ex. 11.

Dr. Angelides contested the materiality of the statements in the grants on the basis that ORI had misunderstood the purpose and applications of his work with anti-peptide antibodies and that the statements about these antibodies were "not integral" to the grant applications or "purely optional" because alternative reagents could have been used. Ang. Br. at 249-50, 254-57; Ang. R. Br. at 231-35. This argument is unsupportable both legally and factually.

As a legal matter, Dr. Angelides cited no authority to support the premise that an intentionally false statement is immunized from consideration as scientific misconduct merely because it is not integral or requisite to the grant application or paper at issue. Such a proposition would permit a scientist, with impunity, to knowingly make false claims that overstate the capabilities or achievements of a laboratory, as compared to others that may also be seeking funding in a very competitive funding environment, so long as the misrepresentations in a particular grant were not about that grant's central project or so long as the scientist could suggest alternative approaches making the falsified data "optional." The integrity of the funding process, which depends on accurate and honest information, could be undermined. The pertinent factors that may be considered in evaluating grant applications generally may include "the scientific merit and significance of the proposed project, the competency of the proposed staff in relation to the type of research involved, the feasibility of the project, [and] the likelihood of its producing meaningful results." 42 C.F.R. § 52.5(a). Hence, any statement included in a grant application that portrays to the reviewers the capacities or accomplishments of the researcher or laboratory as further advanced than they are in reality, or presents a more favorable picture of the likelihood of success than the true facts would suggest, can therefore be considered as material to the funding decision, whether or not it was "necessary" to the presentation of the research proposal. At the same time, it is evident as a general proposition that the more favorable and the more significant the false statement is, all other things being equal, the greater the likelihood that the misrepresentation is intentional.

Turning to the facts of the present case, Dr. Angelides failed to show how any alleged misunderstanding by ORI about the intended uses of the antibodies would mean that his claims about them in the grants were so insignificant as to make it improbable that he would lie about them. The text of the grant applications, excerpts of which were quoted at some length above, in

itself establishes that the battery of anti-peptide antibodies was intended for structural studies of the sodium channel and to "further dissect the cellular distribution" of the various subtypes. See, e.g., Record Ex. 9, at 24; Record Ex. 8, at 24. Furthermore, the one funded grant application stated that revisions were made in response to the reviewers' critique. Record Ex. 8, at 19. Among the changes reported as additional work since the critique was preparation of additional sequence- and subtype-specific anti-sodium channel antibodies (both against synthetic peptide and fragments expressed in yeast). Id. There is thus, as a factual matter, clear evidence of materiality even under the kind of criteria Dr. Angelides appeared to apply.

The Panel received additional testimony supporting the internal evidence from the grant applications suggesting that development of a battery of anti-peptide antibodies was important. Based on his own research, Dr. Waxman testified: "These antibodies would have been a very useful tool to study sodium channel expression. Localization of various sodium channel subtypes, using such antibodies, would have been a significant accomplishment in the field at that time." Waxman WD at 18. Dr. Waxman testified that he had relied on Dr. Angelides's claims to him about the existence, utility and characterization of the anti-peptide antibodies in proposing his own further work in his grant application. Id. at 16-19; see ORI Ex. 77. Dr. Patrick said that the development of a battery of site-specific antibodies would be significant because it would permit targeting sequences specific for the subtypes of sodium channel and different regions of the predicted structure, which would be a major accomplishment and would have been "known and celebrated by all members" of the laboratory.[43] Patrick WD at 51-52, 56. He also testified that the misrepresentations about the production of the anti-peptide antibodies would have "significantly enhanced the likelihood" of a favorable review by the NIH peer review committee. Id. at 55. Dr. Gilbert testified that a battery of different antibodies to various peptides would have been "a powerful tool to study the sodium channel," providing the possibility of distinguishing among different regions of the protein and therefore of greater potential utility than a few anti-peptide antibodies. Gilbert WD at 94. Dr. Elmer testified that "development of a battery of anti-peptide antibodies capable of recognizing different sites on identified regions of the sodium channel protein would have been a significant research tool because it would permit a more detailed study of the various regions and sub-types of the sodium channel." Elmer WD at 78-79.

Dr. Angelides attacked the credentials of both Dr. Patrick and Dr. Gilbert to offer expert testimony on the potential significance of anti-peptide antibodies to work on the sodium channel protein on the grounds that they did not demonstrate sufficient familiarity with the sodium

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[43]Dr. Angelides challenged the basis for this testimony on the grounds that Dr. Patrick was never in his laboratory and, furthermore, did not work specifically on the sodium channel. Ang. Br. at 254-55, and n.188. However, Dr. Patrick's testimony is corroborated in part by Dr. Timothy Benke, who was in Dr. Angelides's laboratory (with some gaps) between May 1989 and December 1993, and who agreed that such success by Mr. Lewallen in his research efforts "would have been the kind of thing that would have been discussed" by the laboratory members. Benke WD at 2, 10.

channel system or work in his laboratory to become aware of his intended applications for this work. Ang. Br. at 255-56. Therefore, Dr. Angelides argued that Dr. Gilbert's statement was "complete nonsense and has no scientific depth of understanding." Ang. Br. at 248, n.183. The Panel found, to the contrary, that both Dr. Gilbert and Dr. Patrick demonstrated relevant expertise to knowledgeably interpret the purpose of the experiments reported and proposed in the grant applications. See Gilbert WD 1-5; Patrick WD at 2-6; ORI Exs. 96, 99. For example, in 1989 when many of these grants were submitted, Dr. Patrick was the head of the Neurosciences Division at Baylor and it is uncontested that he worked on related questions on ion sodium channels and acetylcholine receptors, including extensive use of antibodies. Patrick WD at 1-3. Furthermore, Dr. Angelides did not present any conflicting expert testimony that might have substantiated his allegation that the claims made about anti-peptides antibodies in his grant applications were somehow insignificant or immaterial to the funding sought. Finally, in his brief, Dr. Angelides offered the explanation that the reason he proposed the studies in the grant applications was to seek another application for these reagents, which had not performed as hoped in some situations. Ang. Br. at 253-54. However, even were that the case, Dr. Angelides did not offer a persuasive reason that the alleged misunderstanding by ORI or the expert witnesses about the intended uses of the antibodies would mean that the claims about them in the grants were so insignificant as to make it improbable that the misrepresentations were intentional, when the evidence shows that most of the antibodies simply did not exist.

The Panel concluded that the charges of intentional misrepresentation and falsification concerning anti-peptide antibodies in the text and appendix tables in the grant applications were supported by the preponderance of the evidence.

3. Additional arguments offered by Dr. Angelides on this issue

Dr. Angelides argued that intentional misrepresentation was unlikely, because he "did not hide the fact that the anti-peptide antibodies were not useful for the studies for which [they] were initially intended," but on the contrary, "advised the reviewers that most of the anti-peptide antibodies were useless for the studies for which they were intended." Ang. Br. at 252. He pointed to language in some of the grant applications that reported disappointment with some of the antibodies for certain purposes. Ang. Br. at 252-53. However, in each case where limitations are reported about the utility of the anti-peptide antibodies, the same grant applications report some countervailing positive information which is equally unsubstantiated. Thus, grant application NS28072-01A1 reported that "while the anti-peptide antibodies show some selectivity on immunoblots, we have found that these antibodies typically have very low titers, and in general we have been disappointed with their use and specificity for immunocytochemistry." Record Ex. 8, at 24. However, immediately afterward, the same grant reported that the "antibodies generated against NaCh-subtype fragments expressed in yeast . . . have produced high-titer subtype-specific antibodies. These antibodies have been very useful and specific in immunoblots, immunoprecipitations, and immunocytochemistry on cryostat sections." Id. Similarly, the deferral submission for NS24606-05 reported: "When we synthesized peptides and prepared antibodies our goals were to have a battery of antibodies that

could be used for biosynthetic studies, cellular localization of the different forms of the channel, and to map NaCh topology. Unfortunately, all of the antibodies, save for one, were useless at the ultrastructural level and could not be used for localization or topology studies." Record Ex. 11, at 25. In the next sentence, however, the deferral submission reported that "nearly all anti-peptide antibodies immunoblot and some immunoprecipitate NaChs with varying efficiencies." Id. In any case, the essential point is that a qualified misrepresentation about the limited utility of non-existent antibodies for particular purposes still misrepresents the very existence of the antibodies.

Much of Dr. Angelides's argument in his brief consisted of attacking the documentation of the antibodies whose existence ORI conceded. Ang. Br. at 259, n.190, 260-67. By accepting the claims about the unchallenged antibodies, Dr. Angelides argued, ORI "has been entrapped in the same issue as Dr. Angelides with respect to Mr. Lewallen's representation of his progress." Ang. Br. at 266. He argued that Mr. Lewallen had not produced sufficient documentation that the antibodies he said he had produced were positive in immunoblots.[44] The Panel found this reasoning circular and disingenuous. By arguing that ORI had inadequate evidence to accept the claims about even the unchallenged antibodies, Dr. Angelides seemed to have overlooked, in his effort to attack Mr. Lewallen's credibility, the fact that he was also further undercutting any basis for his claims in grant applications. After all, Dr. Angelides, not ORI, put forward the affirmative assertions about all of these antibodies as true and founded on research data.

Dr. Angelides also raised a defense of honest differences in interpretation, arguing that a reasonable principal investigator "when presented with the data [specifically Western blots] and given the context that he had knowledge that the peptides had been made, would have believed that the data was derived from those peptides." Ang. Br. at 264. He argued that he might especially have assumed that the antibodies had been produced given the unexplained delay between the synthesis of the peptides in 1988 and the second round of injections in 1990. Id.

An honest interpretation defense depends necessarily on a showing that data existed that could have honestly been interpreted as reported, even if another interpretation is possible or preferable. The difficulty with this argument here is the absence of any basis to believe that Dr. Angelides was presented with any data relating to the contested antibodies on which to exercise

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[44]Specifically, in the case of antibody 7671 (corresponding to SP5), Dr. Angelides argued that the only immunoprecipitation testing it on March 4, 1988 was not positive. Ang. Br. at 266; Hearing Ex. 51. The record does not support either the assertion that this experiment did not show reactivity or that it was the only evidence of positivity for this antibody. See Hearing Ex. 51; Record Ex. 1, at Enc. II.C.4.69; ORI R. Br. at 75, n.84. Before Baylor, Dr. Angelides asserted that the antisera which he had retained had been tested periodically but had not yielded positive results. See, e.g., Record Ex. 19, at 482-85. However, he provided no specific information as to which antisera were retained and which were tested and no data in support of these assertions, which, in any case, only support ORI's position that Dr. Angelides did not have a battery of functional anti-peptide antibodies.

judgment. Dr. Angelides did not present any documentation to support even the basis for his claimed "knowledge" that the disputed peptides were synthesized, much less that functional antibodies had been produced and tested on Western blots. At best, Dr. Angelides bolstered this position by arguing, essentially, that the absence of records did not prove their non-existence. Thus, Dr. Angelides contended that "ORI has not produced any evidence that the peptides for which they have been unable to find records were not injected." Ang. Br. at 262. Dr. Angelides rejected the testimony of Dr. Patrick and Mr. Lewallen that their reviews of the peptide synthesis records showed only the peptides to which Mr. Lewallen had testified, but he did not himself offer the peptide synthesis records into evidence or specify any other peptides at issue that were shown in them. See Ang. Br. at 261; Lewallen WD at 29; Patrick WD at 53-54. Dr. Angelides asserted that other peptides might have been synthesized elsewhere, such as at the Baylor peptide core facility, but provided no documentation showing such synthesis of any peptide at issue. Ang. Br. at 261-62. It is hardly a sufficient basis to support Dr. Angelides's claims about the existence and properties of the disputed antibodies for him to show merely that it was possible for peptides to have been synthesized. Furthermore, Dr. Angelides did not provide data in his response to the Baylor Report to show that specific additional peptides had been synthesized elsewhere, even though the Baylor Report presented the same information about the synthetic peptides and the information should have been fresher in Dr. Angelides's mind at that time. See Baylor Report at 192; Ang. Resp. to Baylor Report passim.

Dr. Angelides also argued that the anti-peptide antibodies must have existed because Mr. Lewallen sent them to Drs. Black and Waxman, and they reported the use of these antibodies in their grant applications. Ang. Br. at 273-75. Thus, Dr. Angelides contended, either Mr. Lewallen did have the antibodies about which Dr. Angelides said Mr. Lewallen told him, or Dr. Waxman never got them and did not carry out the experiments reported in his grant. Id. However, the record reflects that Dr. Angelides, not Mr. Lewallen, provided the anti-peptide antibodies to Drs. Black and Waxman. In a cover letter to them signed by him and dated July 17, 1989, Dr. Angelides stated that he was forwarding two anti-peptide antibodies (identified by rabbit number as 7671 and 7738, which correspond to SP2 and SP5) and that, although he has "several others," these look the "most promising of all the anti-peptides" although they have low titers and although he does not know if they "will stain." ORI Ex. 91. Hence, far from supporting any claim by Dr. Angelides that Mr. Lewallen was misleading Dr. Waxman or that Dr. Waxman was making false reports, the evidence in the record on this point strongly corroborates Mr. Lewallen's testimony that, as of 1989, he had tried to develop anti-peptide antibodies to several peptides (specifically including SP2 and SP5), and that only one or two were potentially positive. Further, this letter contradicts Dr. Angelides's present claim that there was no positive data on 7671 (SP5). Dr. Angelides also provided a collaborative letter to Dr. Waxman in September 12, 1989 in which he asserted that he had "fully characterized antibodies generated against synthetic peptides derived from the primary sequences of rat brain sodium channels I, II and III, as well as subtype-specific protein fragments obtained from expression in yeast of cDNAs encoding each channel subtype." ORI Ex. 77, at 44. However, Dr. Waxman testified that the anti-peptide antibodies never proved useful in his hands. Waxman WD 17-19.

4. Conclusion on textual claims and table of anti-peptide antibodies

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for false statements about the existence of 15 anti-peptide antibodies. Specifically, the antibodies designated as SP10, SP13-SP20, SP22 and SP23 in the text and in the table presented in the appendices in grant applications NS24606-05 and the later deferral submission for that grant, NS28072-01A1, and GM48816-01 did not exist. Therefore, all statements about the nature and properties of these antibodies were false. In addition, the three antibodies to sodium channel fragments expressed in yeast that are listed in Table II of NS28072-01A1 (and discussed in the text) did not exist, so all statements about the nature and properties of these antibodies were false. Further, at most four anti-peptide antibodies (designated as SP1, SP3, SP5, and SP21) may have shown any positive reactivity on immunological tests, so that the claims made about the other anti-peptide antibodies (SP2, SP4, SP6-SP9 and SP11-SP12) were false. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides acted intentionally to misrepresent these facts. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive, and the conduct proven constituted scientific misconduct.

C. <u>Appendix Figure 2 of NS28072-01A1</u>

Appendix Figure 2 of grant application NS28072-01A1 presented data that purported to be from Western blot tests of six functional anti-peptide antibodies. Record Ex. 8, at A20. The first three lanes were described as tests of antibodies to specific sodium channel fragments expressed by cDNAs in yeast. The last three lanes were described as tests of antibodies to specific synthetic peptides of the sodium channel. The grant application asserted that these data demonstrated that the antibodies were "very useful and specific in immunoblots, immunoprecipitations, and immunocytochemistry on cryostat sections." Record Ex. 8, at 24.

It is not contested that the primary data for the lanes presented as testing the reactivity of six anti-peptide antibodies were located in data from three unrelated experiments, all which were conducted by Dr. Elmer and none of which involved any of the anti-peptide antibodies. Ang. Br. at 299; Ang. R. Br. at 244. In his response to the charge letter, Dr. Angelides asserted that "[t]he photograph for Figure 2 of the NS28072-01A1 application was provided by Mr. Lewallen." Ang. Resp. to Charge Letter, at ¶547. At the hearing, Dr. Angelides testified that Dr. Wible "assisted in the preparation and provided the data that is contained in Figure 2." Tr. at 1582. It is uncontested that none of the original data for these lanes belonged to Dr. Wible or Mr. Lewallen. Both Dr. Wible and Mr. Lewallen denied any role in the preparation of this figure. Tr. at 2093 (Lewallen); Tr. at 2072 (Wible). We therefore consider first the directly-conflicting testimony of Dr. Angelides and the two other scientists as to who provided the data presented in Figure 2. We next consider whether the uncontested misrepresentations in the legend as to the nature of the data were intentional.

1. Primary data for the lanes in Appendix Figure 2 of NS28072-01A1

A copy of the primary data for the first experiment from which Figure 2 was constructed is at Record Exhibit 1, at Enc. II.C.5.16. Three lanes from that experiment (numbered 1-3 in the original data) were presented as lanes 1-3 in Figure 2. However, in the primary data, the three corresponding lanes are clearly labeled in Dr. Elmer's handwriting as "Mab vs. GP." Dr. Elmer testified that this notation meant that he "was using the monoclonal antibodies (mAb) [to the intact sodium channel] against glycoprotein antigen (GP)." Elmer WD at 82.

The primary data for lanes 4 and 5 of Figure 2 were located in another experiment of Dr. Elmer. Hearing Ex. 27; see also Record Ex. 1, at Encs. II.C.4.21 and II.C.4.28. There was considerable dispute in the record about how to interpret this experiment, which Dr. Elmer testified was an "Olmsted" experiment involving polyclonal antibody 7493, and we address this experiment in more detail in the section relating to intact sodium channel antibodies. See Elmer WD at 17-19; Tr. at 1423-33 (Angelides); Tr. at 2026-29 (Elmer). It was undisputed, however, that the experiment did not involve synthetic anti-peptide antibodies.

Lane 6 was from yet another experiment of Dr. Elmer's for which the primary data were clearly labeled as testing polyclonal antibody 7493 against P3 synaptosomes. Record Ex. 1, at Enc. II.C.4.41. Dr. Elmer confirmed in testimony that the experiment did not involve anti-peptide antibodies but rather the polyclonal antibody. Tr. at 2033.

2. Responsibility for creation and inclusion of Appendix Figure 2 of NS28072-01A1

Dr. Elmer testified without contradiction that he "[c]ertainly . . . did not test six different anti-peptide antibodies and get the positive results depicted in this Appendix Figure 2." Elmer WD at 81. He denied, also without contradiction, having provided his data for use in the grant application. Tr. at 2033. In regard to whether he prepared or provided data for Figure 2, he testified: "This was submitted to the NIH in October 1989, which is more than a year after I had left the Angelides lab for my medical internship. I did not prepare the actual figure or draft the figure legend. I also did not review this grant for accuracy prior to its submission. I never told Dr. Angelides that any of the anti-peptide sera worked this well, and I never heard anyone else make such claims." Elmer WD at 83.

Dr. Wible testified, contrary to Dr. Angelides's contentions, that she did not provide data for or write the legends for the lanes of Figure 2 of NS28072-01A1 relating to the antibodies to peptides expressed in yeast. Compare Tr. at 1582 (Angelides) with Tr. at 2071-72 (Wible). She

further testified that she had not even seen the grant or the figure until the hearing in the present proceeding.[45] Tr. at 2072.

Mr. Lewallen also denied, contrary to Dr. Angelides's contentions, that he participated in preparing the figure or legend or providing the data used to construct the figure. Tr. at 2093; Lewallen WD at 40-42. He denied that he was ever shown the grant or the figure before the Baylor investigation. Id.

Dr. Angelides produced nothing beyond his testimony to substantiate his allegations that Dr. Wible and Mr. Lewallen were the sources of this figure. No data or drafts relating to this figure were shown to have been located in the records of Dr. Wible or Mr. Lewallen. Dr. Angelides produced no evidence that Dr. Wible had any role at all in the preparation of the grant. The Panel concluded in the preceding section that Mr. Lewallen was not responsible for the textual material or table in this grant that made false claims about the anti-peptide antibodies. Dr. Angelides offered no detailed explanation of how the two researchers obtained data from various experiments of Dr. Elmer, together constructed a figure from selected lanes, misrepresented those lanes as involving data from antibodies they did not have, and persuaded Dr. Angelides to accept that figure for use in a grant application. Nor did he offer any explanation of why they would have had any motivation to do so.

The Panel concluded that the responsibility for the inclusion of Figure 2 in the grant application lay with Dr. Angelides, who prepared the grant and signed it as principal investigator and who

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[45]Dr. Angelides argued that Dr. Wible's surprise at the hearing about the claim that she prepared these antibodies was "staged," given her prior responses in her written direct testimony concerning yeast culture systems, which showed she was aware of the issue. Ang. Reply Br. at 242-43. In her written direct testimony, Dr. Wible testified, in response to ORI questions, that she did not "subclone fragments of the different sodium channel genes or use the yeast to produce short peptides" and that she was "not aware of anyone except Mr. Velazquez using the yeast system." Wible WD at 75. She also testified as follows:

> Q. Did you raise or characterize any antisera to sodium channel proteins or peptides?
>
> A. No. I did some immunoprecipitations with Dr. Elmer's 7493 antiserum when trying to translate the type three sodium channel protein, but I did no injection of rabbits or characterization of antisera of any kind. In 1991 I used several antisera to stain transfected cells.

Id. Nothing in this testimony implied that she knew that Dr. Angelides's position was that she had prepared three fragments in yeast, produced and tested antibodies to them, and prepared a figure demonstrating the results that appeared in a specific grant application (NS28072-01A1). The Panel concluded that her testimony that she had not previously been aware of this figure in this grant was credible.

alone had access to all the relevant data. We turn next to whether Dr. Angelides knew that the data he included in Figure 2 were not as he described them.

3. Intentionality of the misrepresentations in Appendix Figure 2 of NS28072-01A1

The most striking evidence that Dr. Angelides knowingly misrepresented the data presented in Figure 2 is his repeated use in various grants of lanes from the same experiments, labeled at times in accord with the notations on the primary data and at other times inconsistently with those notations. We summarize the other uses made of data presented in Figure 2 and how the data are described elsewhere in a table at the end of this sub-section, and discuss them briefly here.

For example, in the NS26672-01 and the later deferral submission for that grant application (which was submitted in September 1988), the data later used in the first three lanes of Figure 2 appeared in the appendix to those submissions as Figure 2B, lanes 1-3, but were identified consistently with the labeling on the primary data as monoclonal antibodies tested on glycoproteins. Record Ex. 1, at Encs. II.C.5.17, II.C.5.18 and II.C.5.19. The identical data were falsely represented in NS28072-01A1 which was submitted on October 26, 1989.[46] Record Ex. 8, at 1, A20.

The data presented in lane 4 of Figure 2 (but printed reversed in orientation from left to right) were also used in a figure in two papers co-authored by Dr. Angelides in which the data were correctly described as an experiment using the 7493 polyclonal antibody but incorrectly described as to the antigen (rat optic nerve rather than synaptosomal glycoproteins). See discussion of Yale papers in regard to intact sodium channel antibodies; see also Record Ex. 1, at Encs. II.C.4.23, II.C.4.24, II.C.5.7, and II.C.5.8. Furthermore, Dr. Angelides used a different lane (also in reverse orientation) from the same Olmsted experiment in a third published paper, again described as using 7493 antibody but claiming a different molecular weight, purity of antigen, and tissue source than shown on the original experimental results. See discussion of Yale papers in regard to intact sodium channel antibodies; see also Record Ex. 1, at Enc. II.C.4.18. These papers were all submitted for publication after Dr. Elmer had left the laboratory and had completed his thesis defense. One of the papers was submitted in February 1989, which was eight months before the grant application containing this figure was prepared, so Dr. Angelides clearly had reviewed and used this experiment before two lanes from it were employed in Figure 2. Therefore, he should have been well aware that the data did not involve anti-peptide antibodies.

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[46]The Panel also noted that the false statements about the data used in Figure 2 generally occurred only after Dr. Elmer defended his thesis in October 1988 and thus had completed his work at Dr. Angelides's laboratory. Hence, the chance of discovery by the experimentalist who might recognize the data or check them against his own records was reduced, and Dr. Angelides's ability to easily misuse data that Dr. Elmer had left with him was increased.

The data presented in lane 6 of Figure 2 were from a Western blot of P3 synaptosomes tested by 7493 antibody. Tr. at 2033 (Elmer); Record Ex. 1, at Enc. II.C.4.41. It is not contested that the same data were used in another location in the same grant application, at Appendix Figure 1C, lane 4, where the lane was described as polyclonal antibody 7493 run against rat sciatic nerve showing a molecular weight of 260 kDa.[47] Furthermore, the same lane was also presented as lane 4 of Figure 3 in the Brain Research paper on which Dr. Angelides was a co-author (and in a draft version of that paper dated March 1989, again before the grant was submitted), described as in Appendix Figure 1C. Therefore, again, the evidence is that Dr. Angelides well knew as of the time he submitted NS28072-01A1 that the data did not involve anti-peptide antibodies.[48]

The evidence demonstrated that Dr. Angelides's attention had been specifically drawn to the true nature of the data from which Figure 2 was constructed. Dr. Elmer testified that he specifically discussed the experiment from which the first three lanes of Figure 2 were drawn with Dr. Angelides many times, so that Dr. Angelides was aware that they were not related to anti-peptide antibodies. Elmer WD at 81-82. As for lanes 4 and 5 of Figure 2, Dr. Elmer testified that the primary data "were generated and photographed in 1987 as part of my experiment using the Olmsted procedure to affinity purify the 7493 antibody. . . . As I have discussed, the two lanes on the right were done with an anti-170-specific antibody fraction isolated from the 7493 antibody. The primary data do not show an experiment with two anti-peptide antibodies as represented in the figure legend of the NS28072-01A1 grant application." Id. at 82-83. He testified that he also discussed this particular experiment with Dr. Angelides. Id. at 19.

Furthermore, a careful review of the original primary data involved demonstrated that it was unlikely that the misrepresentations in this figure could have resulted from honest error. First, the data were in each case clearly labeled as to the antibody being tested. Second, none of the other lanes in any of the experimental arrays from which this figure was constructed contained data relating to the testing of anti-peptide antibodies, further reducing the potential for accidental confusion of any kind.

In addition, the record demonstrates that none of the antibodies whose activity the figure purported to show even existed at the time the grant was submitted. As discussed in the preceding section, the antibodies to fragments expressed in yeast never existed. Mr. Lewallen testified as follows concerning the specific anti-peptide antibodies described in the last three lanes of Figure 2:

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[47]The representations of the tissue source and molecular weight were not consistent with the labeling of the primary data, as is addressed in the section on grant application claims about sodium channel antibodies.

[48]The Panel noted that in a number of instances other lanes of data from the same experiments were also used and falsely described in other locations, which are discussed in more detail in the portion of the decision addressing the sodium channel antibodies.

> These locations would appear to correspond to peptides SP8, SP9 and SP11 in the NS28072-01A1 grant application table II. I had synthesized peptides eight and nine in 1988, but I did not inject them into rabbits until 1990, which was after the date when this grant (10/21/89) was signed by Dr. Angelides. Peptide SP11, my NaCh3C-T, was a peptide that I planned to do, but never synthesized and never injected into rabbits. None of this data was from experiments that I did, and I have no knowledge of these antisera having been raised or tested in the Angelides laboratory in time to be reported in this grant application.

Lewallen WD at 41. The fact that the antibodies to which the data were falsely alleged to relate did not even exist further reduced the possibility that the misrepresentations were unintentional.

The Panel concluded that Dr. Angelides intentionally misrepresented the data reported in Figure 2 and rejected Dr. Angelides's contention that he reasonably relied on information from Dr. Wible or Mr. Lewallen in preparing the figure.

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Summary of Sources and Other Uses of the Data in Figure 2 of NS28072-01A1

Lane	Claim in NS28072-01A1	Source	Use	Use
1	Antibody to NaCh I, residues 461-493, peptide generated in yeast cDNA	II.C.5.16 (Elmer) Mab v. GP Lane labeled 1	NS26672-01 In App Fig 2B (identified correctly)	NS26672-01 Def. (same)
2	Antibody to NaCh II, residues 459-492, peptide generated in yeast cDNA	II.C.5.16 (Elmer) Mab v. GP Lane labeled 2	NS26672-01 In App Fig 2B (identified correctly)	NS26672-01 Def. (same)
3	Antibody to NaCh III, residues 1976-2009, peptide generated in yeast cDNA	II.C.5.16 (Elmer) Mab v. GP Lane labeled 3	NS26672-01 In App Fig 2B (identified correctly)	NS26672-01 Def. (same)
4	Antibody to NaCh I, residues 465-476, synthetic peptide	II.C.4.21/II.C.4.28 (Dr. Elmer's Olmsted experiment using 7493 against glycoproteins) (same data in 4th lane, but flipped left to right)	PSRL Fig 1 Lane b/2 (as 7493 detecting 260MW protein in rat optic nerve GPs)	ANYAS Fig. 1 Lane b/2 (Same as PRSL)
5	Antibody to NaCh III, residues	II.C.4.21/II.C.4.28 (Dr. Elmer's Olmsted		

	1986-2003, synthetic peptide	experiment using 7493 against glycoproteins)		
6	Antibody to NaCh II, residues 467-485, synthetic peptide	II.C.4.41 (labeled 7493 against P3 synaptosomes)	NS28072-01A1 Fig 1C; lane 4 (as 7493 detecting 260MW protein in rat sciatic nerve)	Brain Research a) used in draft -- dated March 1989, in Fig. 1C, as lane 3, (as anti-260 antibody against glycoproteins) b) used in paper in 1990, in Fig. 3, as lane 4 (as 7493 against rat sciatic nerve)

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4. Additional arguments offered by Dr. Angelides on this issue

Dr. Angelides argued that, although he "does not dispute that the experimental lanes and photographic representations of Figure 2 are from Dr. Elmer's experiments," he was nevertheless not "blaming" Mr. Lewallen and Dr. Wible for having provided this figure, because, he asserted, he had seen suitable Western immunoblots of Mr. Lewallen's anti-peptide antibodies and he had reviewed data of "Coomasie blue stained gels of the expressed proteins and immunoblots" that Dr. Wible generated. Ang. Reply Br. at 244; see also Ang. Br. at 299. This argument is without merit in relation to Figure 2. Even if Dr. Angelides had seen other, legitimate data, the data presented here are admittedly not what the identifications claim. Further, any other data Dr. Angelides might have seen relating to anti-peptide antibodies could not have supported the claims in this figure, since these antibodies did not even exist. Further, Dr. Angelides did not explain how Mr. Lewallen and Dr. Wible could have presented data to him from three separate experiments performed by a third member of the laboratory and yet not be to "blame" for misrepresenting the data as relating to non-existent antibodies.

5. Conclusion on Appendix Figure 2 of NS28072-01A1

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the inclusion of Figure 2 in NS28072-01A1. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides acted intentionally to misrepresent the data presented by the figure in the figure legend. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive, and the conduct proven constituted scientific misconduct.

D. Overall Conclusion on Anti-peptide Antibodies Project

The Panel's conclusions on this project were again mutually reinforcing. Thus, the egregious use of data from so many unrelated sources to construct a false table to present the impression of legitimate data resulting from non-existent antibodies further persuaded the Panel that Dr. Angelides acted intentionally and not through honest error or good faith reliance on Mr. Lewallen in making the false claims in the text and tables of the grants discussed in the first sub-section. In addition, the absence of any evidence that the contested antibodies presented in the grant applications were actually used for any applications further supported the overwhelming evidence that they were never produced at all. Finally, the Panel found Dr. Angelides's shifting stance on the roles of Mr. Lewallen, Dr. Elmer, and Dr. Wible disturbing. He both attacked the credibility of their testimony that they never performed the experiments attributed to them to develop the claimed battery of anti-peptide antibodies and placed the responsibility for the admittedly-false figure on Mr. Lewallen and Dr. Wible; yet, he simultaneously denied that he was blaming them or accusing them of misconduct.

III. The Fluorescent Amino Acid Project

A. Introduction on Fluorescent Amino Acids

From 1989 through 1992 Dr. Angelides submitted several grant applications that included a project to introduce fluorescent amino acid derivatives at identified sites on the sodium channel protein so as to permit the use of fluorescence-based physical techniques to probe protein structure and function. The project was inspired by an experiment reported by Dr. Peter Schulz et al. in a journal article published in early 1989,[49] and it combined molecular biology and organic chemistry methods. See Record Ex. 19, at 348. Dr. Barbara Wible was a molecular biologist in Dr. Angelides's laboratory who had worked for him for many years, and she was to perform the molecular biology experiments required for the project.

Dr. Wible's description of the steps necessary to manipulate the sodium channel protein was unchallenged. She described the project as consisting of the following steps:

1. (a) Obtain the sodium channel gene (type III) from Dr. Rolf Joho of Baylor, who had cloned it and shown that RNA made in a cell-free enzymatic reaction using the cloned DNA could be injected into frog egg cells and expressed there; (b) transcribe the gene efficiently; and © show that it could be translated in vitro (i.e., in a test tube).

2. (a) Using site-directed mutagenesis, introduce stop codons (codons that normally tell the protein synthesis machinery to stop synthesizing because the end of a protein has been reached) into the messenger RNA (mRNA) of the sodium channel gene; (b) show that it could still be

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[49]"A General Method for Site-Specific Incorporation of Unnatural Amino Acids into Proteins," Science 244:182-188 (April 14, 1989) (Record Ex. 48).

transcribed efficiently in vitro; and © show that the transcribed mutant RNA could be translated in vitro up to the stop codon.

3. (a) Obtain the cysteine- (cys) and phenylalanine- (phe) suppressor transfer RNA (tRNA) genes cloned by Dr. Jeffrey Miller's lab;[50] (b) transcribe them efficiently; © show that in vitro aminoacylation reactions could be used to charge (attach amino acids to) the transcripts; and (d) show that the products could act to suppress stop codons in an in vitro protein synthesis system (i.e. that the presence of the suppressors would cause the insertion of either cys or phe at the location where protein synthesis would otherwise cease due to the presence of a stop codon).

4. Using a polymerase chain reaction (PCR) machine, alter the cys and phe suppressor tRNA genes so that transcription would produce an RNA two nucleotides shorter than the normal suppressor tRNA.

5. (a) Using organic chemistry, synthesize the pCpA dinucleotide (to replace the two nucleotides deleted from the end of the tRNAs); (b) synthesize the fluorescently labeled amino acid; © chemically attach it to the dinucleotide; and (d) link the product to the truncated suppressor tRNAs by using the enzyme, T4 RNA ligase.

6. Utilize the suppressor tRNAs charged with the fluorescent amino acid in in vitro protein synthesis systems to produce proteins with the fluorescent amino acids incorporated at the position determined by the position of the stop codon in the mutant gene, from step two.

7. Obtain sufficient sodium channel protein in this system such that when incorporated into artificial membranes, its ion channel function could be demonstrated by electrophysiological methods, and the fluorescence associated with the active units of sodium channel could be measured.

8. Measure the changes in fluorescence when sodium channel function was stimulated.

See Wible WD at 8-12.

Dr. Angelides is alleged to have provided falsified data and misrepresented experimental results concerning this project in four figures and text that appear in four grant applications submitted to NIH from December 1989 through January 1992. There are five charges of scientific misconduct concerning this project -- four charges for each of four figures and associated text that appear in

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[50]Although these suppressor tRNAs were produced by Dr. Jeffrey Miller, they were supplied to Dr. Wible by Dr. Murgola of M.D. Anderson of Houston. Thus, any reference to the Murgola genes (which was usually how Dr. Angelides referred to them) should be understood to be those genes produced by Dr. Miller and reported in Normanly, Masson, Kleina, Abelson and Miller, [1986] Proceedings of the National Academy of Sciences 83, 6548-6552 (ORI Exhibit 14). Tr. at 402-03 (Wible).

grant application NS24606-05 Deferral (two of which are also in grant application GM48816-01), and an additional charge regarding unillustrated textual claims in these two grants as well as career grant non-competitive renewals NS01218-04 and NS01218-05. Each of these charges involves claims that Dr. Angelides's laboratory had succeeded in accomplishing critical steps in the project. Dr. Angelides agreed that the primary data for each of the figures were mislabelled in the grants in which they appeared, in both the legends and the related text; he disagreed that there were claims of success in the unillustrated text that were false. The Panel therefore organized its discussion of the charges into those dealing with the figures, which Dr. Angelides agreed are false representations of data that amount to scientific misconduct by whoever created them, and the charges dealing with the unillustrated text, which require our consideration as to whether certain statements are false prior to determining who is responsible and whether any falsifications found were intentional.

Dr. Angelides's general response to the charges about the false figures and related text was that all were given to him for insertion into the first and subsequent grants by Dr. Wible. Dr. Wible categorically denied giving Dr. Angelides any figures, writing any of the text for the grants at issue, or ever telling him that she had succeeded in her experiments. Specifically, she testified that she was never able to manipulate successfully either Dr. Joho's clone to produce mutagenized mRNA or Dr. Miller's suppressor tRNA clones to produce tRNA for the proposed in vitro system for incorporation of the fluorescent amino acid into the sodium channel protein. Wible WD at 14, 68. Dr. Angelides filed an allegation of scientific misconduct concerning Dr. Wible with NIH during the Baylor Sub-Committee's proceedings. Record Ex. 29. The Baylor Sub-Committee exonerated her in its report.

Below, the Panel provides a brief chronology of events relating to these charges, and then outlines the undisputed facts with respect to the four figures (with related text), since Dr. Angelides agreed that the figures were misrepresented. We next proceed to analyze the record to determine who was responsible for creation and submission of these items, and whether the misrepresentations were intentional. We conclude that the preponderance of the evidence establishes that Dr. Angelides, not Dr. Wible, committed scientific misconduct with respect to all these items. We discuss Dr. Angelides's other arguments about the figures and conclude that they do not alter our conclusions about the preponderance of the evidence. Finally, since Dr. Angelides denied that the unillustrated text was false, we review the charges about it separately and conclude that, contrary to Dr. Angelides's contentions, the text does claim success in steps of the project for which no support in the primary data can be found. These false claims made in the context of continuing applications for a multi-year career grant, while not as egregious as those made in the competitive grant applications, were made in the time between NS24606-05 Deferral and GM48816-01 and establish a pattern of scientific misconduct by Dr. Angelides extending over several years, including some time after Dr. Wible was no longer a member of the laboratory.

B. Chronology of events

Dr. Angelides initially proposed the fluorescent amino acid project to NIH in a grant application dated June 28, 1989, NS24606-05. Record Ex. 9. In a November 1989 telephone conversation with Dr. Patricia Jost of NIH, he was informed that the grant application had been deferred for further information. Tr. at 1503. Dr. Angelides convened a meeting in late November or early December with Dr. Wible, Dr. Jones, and Mr. Lewallen to discuss steps needed to satisfy the concerns of the review committee. Tr. at 472 (Wible); see also Tr. at 1505 (Angelides); Tr. at 536 (Jones). Dr. Wible was assigned to proceed with molecular biology experiments for the project while Dr. Jones and Mr. Lewallen did experiments to ensure that the fluorescent signal to be produced by the incorporation of these amino acids would be detectable above background levels. Tr. at 537 (Jones). Dr. Wible testified that she kept Dr. Angelides apprised of her experimental problems and progress but did not furnish him with any data or text for insertion into the resulting revised grant application, NS24606-05 Deferral (Record Ex. 11), that was dated December 29, 1989 (but may not have been mailed until January 2, 1990). Wible WD at 14-15; Tr. at 474. Dr. Angelides admitted that some of the figures were produced at Medical Illustrations during the period Dr. Wible was absent from Baylor for a family Christmas visit; they differed on whether she returned to Houston before the grant application was mailed.[51] The four figures and associated text at issue were additions to the June 1989 version of the grant application. The NS24606-05 Deferral application was not funded.

Dr. Angelides submitted continuing grant applications NS01218-04 (Record Ex. 4) and NS01218-05 (Record Ex. 5) in April 1990 and April 1991, respectively. These applications were part of a continuing career grant. None of the falsified figures appeared in these submissions; the charges of scientific misconduct with respect to these continuation applications relate solely to text claiming success in the project.

Dr. Wible worked in Dr. Angelides's laboratory until June 1991, at which time she left to work in another Baylor laboratory. Dr. Angelides submitted grant application GM48816-01 in January 1992. Record Ex. 13. The grant contained two of the four falsified NS24606-05 deferral figures and similar legend and textual descriptions. Dr. Angelides withdrew GM48816-01 from NIH consideration in July 1992. Angelides Ex. 103.

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[51]Dr. Angelides contended that the Baylor Sub-Committee contaminated the Medical Illustrations files by producing figures of its own during its investigation. We discuss elsewhere the Baylor Sub-Committee's and ORI's handling of the Medical Illustrations. With respect to this particular series of figures, the Panel did not need to find the Baylor files probative of anything since the dispute was over who created the figures, not who took the figures in to the Medical Illustrations facility to be reproduced.

C. The figures in applications NS24606-05 Deferral and GM48816-01

1. Description of Figures at issue

a. Figure 8C of NS24606-05 Deferral

In grant application NS24606-05 Deferral, Figure 8 was described as representing "Engineering of amber $tRNA^{Cys}_{CUA}$ (A) and $tRNA^{Phe}_{CUA}$ (B)." Record Ex. 11. Panel C is described as "PCR products." Page 13 of the text referring to Figure 8C stated, "PCR was performed with the plasmids encoding for the cys (Figure 8A) and the phe (Figure 8B) suppressor tRNAs supplied by Jeffrey Miller as template. PCR products of the correct size (e.g., 84 bp) were isolated on a low melting point agarose gel (Figure 8C)." There are four lanes of data but only three are labeled, respectively, "phe," "cys," no label, and "ladder," with the first two lanes showing bands at approximately the same height. The figure and text purported to show that, using PCR, Dr. Angelides's laboratory had modified the tRNA genes from Miller so that they could effectively transcribe a tRNA in vitro having the normal 3' end, which would ultimately be used to test the ability of the suppressor tRNAs provided by Miller to suppress a nonsense codon in vitro.

It is undisputed that the primary data for this figure were not from a PCR reaction but were from an unrelated experiment conducted by Dr. Wible involving digestion of neurofilament genes with restriction enzymes. Compare Record Ex. 1, at Enc. II.C.2.1 (Figure 8C) with Enc. II.C.2.3 (copy of primary data, original in Hearing Ex. 6). The primary data were on a page of Dr. Wible's notebook and contained a description of the experiment with a Polaroid photograph taped to the page. The photograph, with the descriptions "phe," "cys," and "ladder" added, was used as Figure 8C. There was nothing on the page to suggest that PCR or tRNAs were involved. No copy of Figure 8C was found in Dr. Wible's laboratory notebook or files. A photocopy of Dr. Wible's laboratory notebook page with the experiment and data accurately portrayed was found in a file of Dr. Angelides for a successor grant, GM48816-01. (Although Figure 8C does not appear in GM48816-01, the associated PCR experiment claim was included there.) Dr. Angelides agreed that Figure 8C and its descriptions were falsely presented.

b. Figure 12 of NS24606-05 Deferral

This figure was described in its legend as "engineering and in vitro transcription of $tRNA^{Cys}_{CUA}$ where 3'CA is deleted for chemical misaminoacylation." Record Ex. 11, at 17. The corresponding text states, on page 16 --

> [F]or Cys tRNA, PCR was performed with oligonucleotides at the 3' end of the gene that included a PstI site to both define the end of the transcription unit and to facilitate cloning into pSP65. (Figure 12). The end result is a tRNA transcript 2 nucleotides shorter that the full length transcript which can function as a substrate for chemical aminoacylation.

This figure and its corresponding descriptions purport to show that Dr. Angelides's laboratory had succeeded in shortening the cys tRNA gene by two dinucleotides so that the fluorescent amino acid attached to a synthetic dinucleotide (pCpA) could be ligated to the transcript, i.e., that step 4 of the project had been completed successfully.

This figure was made up of a portion of a Polaroid photograph found in Dr. Wible's laboratory notebook on a page dated December 4, 1989 with the addition of an arrow pointing to a distinct band. Compare Record Ex. 1, at Enc. II.C.2.2 with Enc. II.C.2.4 (primary data in Hearing Ex. 6). The page included with the photograph a description of the experiment involved, a restriction endonuclease digestion of plasmids containing tRNA genes, not a transcription of tRNA genes. The products displayed on the gel in Figure 12 are DNA, not RNA; they were generated by digestion, not PCR amplification. (Copies of the relevant pages of the notebook appear as ORI Ex. 20.) No copy of Figure 12 was found in Dr. Wible's laboratory notebook or files. As with Figure 8C, a photocopy of Dr. Wible's laboratory notebook page with the experiment and data accurately portrayed was found in Dr. Angelides's file for the successor grant GM48816-01. (Although Figure 12 does not appear in GM48816-01, the claim that the tRNA had been successfully shortened was included there.) Dr. Angelides agreed that the figure and accompanying descriptions are inaccurate.

c. Figure 10 of NS24606-05 Deferral and Figure 5A of GM48816-01

The figure legend for this figure in both grant applications described the figure as --

> Suppression of TMV translation by $tRNA^{Cys}_{CUA}$. In vitro translations were done under standard conditions with 100 ng of TMV mRNA in rabbit reticulocytes in the presence of ^{35}S-Met. Translation products were electrophoresed on 7.5% polyacrylamide gels and autoradiographed. Lane 1 TMV mRNA, lane 2 TMV mRNA with 300 ng of in vitro transcribed $tRNA^{Cys}_{CUA}$, lane 3 TMV mRNA with 100 ng of $tRNA^{Cys}_{CUA}$.

Record Ex. 11, at 15; Record Ex. 13, at A-7. The textual claims in the two grants were not identical. Specifically, the text of the NS24606-05 Deferral stated, "Most importantly, the tRNAs that we engineered are also active, because translation of TMV mRNA which has an amber termination codon can be suppressed (Figure 10) and a larger protein made . . . ." Record Ex. 11, at 15. The corresponding text of the later GM48816-01 stated --

> So that we could attach the chemically misacylated amino acid pCpA directly to the acceptor stem of the suppressor tRNA using T4 ligase we engineered a shortened cDNA where the 3' end CA were deleted to which we then ligated duplex oligonucleotides containing T7 polymerase promoter sequences. The end result is a tRNA transcript 2 nucleotides shorter than the full length transcript which can function as a substrate for chemical aminoacylation. From 250 ml of transcription mixture, we have obtained 100 mg of $tRNA^{Cys}_{CUA}$. Without too much difficulty we

> have scaled this reaction up to 2.5 ml where we have obtained almost 1.0 mg of suppressor tRNA. Most importantly the tRNAs that we engineered, after ligating CA ends, are also active, because translation of TMV mRNA, which has an amber termination codon can be suppressed (Fig. 5A, Appendix) and a larger protein made.

Record Ex. 13, at 22. Thus, the later grant contained a specific claim that the tRNAs had been shortened and then aminoacylated, and that the experiment had been conducted at least twice, with specific volumes of suppressor tRNA obtained.[52]

On page 22 of NS24606-05 Deferral, the grant application stated --

> In experiments with TMV at 100 ng (an intermediate concentration) of amber Cys tRNA, we have observed that a read-through protein is made (Figure 10), with an efficiency of 30% (Figure 10, lane 1) and a 3-fold increase in the concentration of the suppressor appears to increase its efficiency to 45% (Figure 10, lane 2).

Record Ex. 11, at 22. In effect, the figure and associated text represented that Dr. Angelides's laboratory had succeeded in an important step in the project, engineering a suppressor tRNA that could be successfully translated. The further description of the experiment found in the GM48816-01 grant application stated --

> [I]n microsomes we have used a high concentration of the fluorescently labeled suppressor tRNAs to increase the yield of read-through product. In experiments with TMV at 100 ng (an intermediate concentration) of amber Cys tRNA, we have observed that read-through protein is made (Figure 5) with an efficiency of 30% (Figure 5, lane 1) and a 3-fold increase in the concentration of the suppressor appears to increase its efficiency to 45% (Figure 5, lane 2).

Record Ex. 13, at 29. Thus, the later grant claimed that this experiment was performed using fluorescently labeled suppressor tRNAs.

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[52]Dr. Angelides contended that grant application GM48816-01 contained an inconsistency between the legend for Figure 5A and the textual references to the figure that is "clearly inaccurate and a mistake," and therefore not a falsification, as ORI charged. Ang. Br. at 82. He claimed, "A reviewer reading the legend of Figure 5A will clearly see that the figure describes an unmodified suppressor tRNA and not a suppressor tRNa with the CA end deleted." Id. The Panel did not agree with Dr. Angelides that the figure legend and text would have been obviously inconsistent to a reviewer. The text appears to define $tRNA^{Cys}_{CUA}$ as the product of the process to modify the suppressor tRNA, and both the figure legend and the text refer to the use of $tRNA^{Cys}_{CUA}$ in the experiment being reported.

The primary data for this figure were found in an autoradiogram from an experiment from Dr. Wible's laboratory notebook in which she used a TMV translation method to test whether the suppressor genes were working. Record Ex. 1, at Enc. II.C.8.a (original is Hearing Ex. 29, retained in Hearing Ex. 6).[53] (Since the ultimate goal of the project was an in vitro synthesis system, it was necessary to ascertain whether the suppressor genes that had previously only been used in an in vivo system were working. See step 3(d) above; Wible WD at 41.) Dr. Wible testified that the experiment did not work, and the Panel's review of the experimental protocol and the data confirmed that testimony. Wible WD at 43; Hearing Ex. 6. Lanes 2 and 3 of the figure are from the autoradiogram; lane 1 does not appear among the other lanes on the autoradiogram and its origin is unknown. Thus, the figure is clearly falsified as to its representation that all three lanes were from the same experiment. There is a wax pencil box around the two lanes on the original autoradiogram that were apparently placed there to define for Medical Illustrations what portion of the data should be photographed. Both Dr. Angelides and Dr. Wible attributed the placing of the wax pencil marks on the autoradiogram to each other. Tr. at 1524-28 (Angelides); Wible WD at 41. A photograph of the autoradiogram was also found in Dr. Angelides's file for the GM48816-01 grant application. In his statements to the Baylor Sub-Committee, Dr. Angelides agreed that the figure did not accurately reflect the primary data.[54] Record Ex. 23, at 126.

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[53]The autoradiogram is unlabeled except for a notation that it was a three-hour exposure, but the Panel was able to confirm by visual inspection that the data in the lanes represented there corresponded with an autoradiogram marked "12/20/89 o/n [overnight] exposure" (Record Ex. 1, at Enc. II.3.8.b, original is Hearing Ex. 29), which appeared in the notebook after the unlabeled autoradiogram and had the lanes marked in a manner corresponding with the experiment's description.

[54]In his testimony before the Panel, and in his post-hearing brief, Dr. Angelides stated that he could not tell whether the figure was false because he found Dr. Wible's laboratory notebook confusing. Tr. at 1639; Ang. Br. at 105. In addition, Dr. Angelides took the position that Dr. Wible lied when she said that she never succeeded in this step of the project. Dr. Angelides never identified any items in the notebook that would support an interpretation of the primary data consistent with the figure legend, nor any data that would support his position that Dr. Wible successfully aminoacylated the suppressor tRNAs in the fashion described in the figure legends or text. The Panel examined the relevant pages of the notebook and determined for itself that, even if the unlabeled version of the primary data was used (which the Panel considers doubtful, as the labeled version is a better match for the figure), the figure was definitely false, since the experimental results associated with the primary data clearly showed that the suppression did not work, and since there was no evidence in the notebook preceding the submission of NS24606-05 Deferral, or even in the months following that submission, that Dr. Wible ever succeeded in these experiments. Since Dr. Angelides contended that this figure and its associated text were given to him by Dr. Wible, like the other figures in NS24606-05 Deferral, the Panel included them in its overall analysis of how all these false figures came to be created and submitted to NIH.

d. Figure 11 of NS24606-05 Deferral and Figure 5B of GM48816-01

These two figures are identical and are described in substantially the same terms in their respective figure legends --

> Aminoacylation of in vitro transcribed $tRNA^{Cys}$ with E. coli synthetases. Three hundred ng of in vitro transcribed $tRNA^{Cys}_{CUA}$ was added to 30 units of E. coli synthetases in the presence of ^{35}S-cysteine and the reaction proceeded for two hours at 37^0C. The products were precipitated by ethanol and applied to a 12% polyacrylamide/7M urea gel and autoradiographed.

Record Ex. 11, at 15; Record Ex. 13, at A-8. The additional text for each grant varied only slightly. In NS24606-05 Deferral, the text stated, on page 15, ". . . and the $tRNA^{Cys}$ can be charged with ^{35}S-cysteine (Figure 11, below)." In GM48816-01, the additional text on page 22 stated, "In addition the $tRNA^{Cys}$ to which CA has been relegated can be charged with ^{35}S-cysteine (Fig. 5B, Appendix)."

This figure and text purports to show an experiment demonstrating that Dr. Angelides's laboratory had succeeded in generating a suppressor $tRNA^{Cys}$ by in vitro transcription from a cloned tRNA gene and chemically linked to radioactive cysteine by the normal enzymes (synthetases). While this was not one of the steps integral to the project, it was an experiment showing that the tRNA was capable of serving as a substrate for protein production despite the genetic engineering required to ligate the fluorescent amino acid.

Dr. Wible testified that she had not attempted such an experiment at the time NS24606-05 Deferral was submitted. Instead, the primary data for these figures came from an experiment conducted by Dr. Wible on December 11, 1989 for in vitro transcription to synthesize tRNAs from cloned tRNA genes present on plasmids. Wible WD at 43; see Record Ex. 1, Enc. II.C.3.6 (original in Hearing Ex. 6). Thus, the experiment did not involve an aminoacylation reaction that resulted in the charging of the tRNA with radioactive cysteine. Dr. Wible's notebook contained autoradiograms from this experiment showing radioactive RNA products separated by size. The figure was falsified by showing the primary data upside down, with the result that it appeared that there was a band representing the cysteine linked to the tRNA that had migrated farther than the free cysteine. Compare Record Ex. 1, at Enc. II.C.3.2 with Enc. II.C.3.6. Medical Illustrations photographed the autoradiogram and delivered it to Dr. Angelides on December 28, 1989. A photograph of the autoradiogram, with the handwritten identifying labels that appear in the primary data removed, was also found in Dr. Angelides's file accompanying the GM48816-01 grant application. No such photograph was located in Dr. Wible's records. Dr. Angelides admitted in his testimony before the Baylor Sub-Committee that the figures and corresponding text did not accurately reflect the primary data.

2. Responsibility for the creation and submission to NIH of grant figures relating to fluorescent amino acid project

Dr. Angelides contended that all of the figures and associated text as they appeared in the grants had been given to him by Dr. Wible when NS24606-05 Deferral was being prepared. Tr. at 1464. Specifically, he maintained that the figures were given to him separately from the primary data used to assemble them, and that he had no way of knowing that they were not what Dr. Wible claimed that they were. Tr. at 1508-09. Dr. Wible testified that she had never seen these uses of her data until she was shown NS24606-05 Deferral by the Baylor Sub-Committee. Wible WD at 16. She also testified that she did not realize until late December 1989 that she would be required to create suppressor tRNAs with two dinucleotides deleted from the ends by using PCR. Id. at 13. She testified that she did not even attempt such a PCR experiment, including ordering the oligonucleotides needed, until she returned from Christmas vacation in January 1990. Id. at 15. Dr. Wible stated that she never got functional suppressor tRNAs because her PCR experiments were never successful, and consequently she never attempted aminoacylation of the fluorescent amino acids. Id. at 26, 45. Thus, the project's progress was essentially halted at step 2 of the process. Dr. Wible testified unequivocally that she made Dr. Angelides aware of each step of her experiments and he knew that she had never succeeded; if she had, the laboratory would have published the results. Tr. at 473.

The Panel independently reviewed the figures and the primary data, and found that these figures are certainly all false. Moreover, there was no claim of honest error or difference of opinion presented for the Panel's evaluation. Consequently, since he claimed that he placed the data and text into the grant applications based solely on Dr. Wible's representations, Dr. Angelides's repeated argument that he lacked the molecular biology background to assess these data is irrelevant. Instead, the Panel was required to weigh the credibility of competing accounts of the drafting process for this grant. Dr. Angelides claimed that he unquestioningly accepted from Dr. Wible several figures and text claiming that substantial progress had been made in this ambitious project; thus, it was she who committed scientific misconduct, since she knew that the false information would be submitted to NIH in support of a request for funds. Ang. R. Br. at 145-49. Dr. Wible contended that she did not provide figures or draft text for the grant applications claiming success in any of the steps of the project, but that she helped Dr. Angelides develop the idea for the project, kept him apprised of her progress through oral reports and review of experimental results recorded in her laboratory notebook, shared relevant journal articles, and told him her analyses of how to overcome problems in the project. Wible WD at 20; Tr. at 436-37. The Panel reviewed the record and concluded that the preponderance of the evidence indicated that Dr. Angelides, not Dr. Wible, was responsible for creation and submission to NIH of these falsified data. We first discuss the evidence that led us to this interpretation of events and then address the evidence that disfavors the scenario propounded by Dr. Angelides.

Dr. Angelides argued that although he signed these grants as principal investigator, he was not knowledgeable enough about molecular biology to recognize that the figures and associated text allegedly given to him by Dr. Wible for presentation in the applications were false. Tr. at 1507-09. The most compelling evidence that Dr. Angelides had direct and accurate knowledge of the nature of Dr. Wible's data was the photocopies of pages with all the experiments and data accurately portrayed, which the Baylor Sub-Committee found in December 1992 in Dr.

Angelides's file accompanying his copy of grant application GM48816-01. While before the Baylor Sub-Committee, Dr. Angelides stated that he received the photocopy of the notebook page containing the photograph used in Figure 8C from Dr. Wible and placed it in a file at the time he was preparing NS24606-05 deferral, but he did not ever look closely at it until it was brought to his attention by the Baylor Sub-Committee. Record Ex. 19, at 385. Other pages showing the primary data for the other falsified figures were similarly identified. Before this Panel, Dr. Angelides now alleges that the pages must have been added to this file by Dr. Wible or by the Baylor Sub-Committee after the file was confiscated by Baylor, and that he must not have put them into this file because it did not make sense to include in it data for NS24606-05 Deferral Figures 8C and 12, which did not appear in the GM48816-01 grant application. See, e.g., Ang. Br. at 66-67, 97.

The Panel has examined the transcript of Dr. Angelides's discussion of the GM48816-01 file with the Baylor Sub-Committee and concluded that his recent assertion that the photocopies were inserted into this file after the confiscation of his files is not credible. Although it was clearly critical to his case, Dr. Angelides did not initially challenge the file's contents as something that he did not recognize as part of his records. Instead, he identified them as something he had seen before but not thoroughly examined. Dr. Angelides discussed this file in this manner in his appearances before the Baylor Sub-Committee on September 30, 1993 (Record Ex. 19, at 382-385, 429-33), November 2, 1993 (when he appeared jointly with Dr. Wible) (Record Ex. 23, at 125-133, 162-165), and November 1, 1993 (when he appeared jointly with Mr. Lewallen) (Record Ex. 21, at 19-21). Given this history, the Panel did not credit Dr. Angelides's current contention that he provided the photocopies of laboratory notebook pages to the Baylor Sub-Committee and they were somehow recycled into the file after it was confiscated, or his allegation that Dr. Wible may have added the photocopies of her laboratory notebook pages to the file during her testimony before the Baylor Sub-Committee. Ang. Br. at 60-61, 74-75, 86-87. In addition, Dr. Angelides's acknowledgment before the Baylor Sub-Committee of the GM48816-01 file and its contents as his own discredits his argument that the inclusion of data in the file for two figures that were used in the NS24606-05 Deferral grant application but not in GM48816-01 somehow demonstrated that these data were placed in the file by Dr. Wible or the Baylor Sub-Committee. Moreover, although Dr. Angelides did not include these figures in the GM48816-01 grant application, the results claimed in their figure legends were still contained in that grant.

Although the exact date of Dr. Wible's return to Houston from Christmas vacation was disputed, the Panel found that her admitted absence gave Dr. Angelides the opportunity to use her laboratory notebook without interruption. In addition, Dr. Angelides had particular knowledge of the grant review committee's concerns and was facing a deadline for responding to those concerns in a manner that demonstrated that his laboratory could produce the results predicted in the June 1989 version of grant application NS24606-05.

Other than Dr. Angelides's testimony, there was no evidence that Dr. Wible participated in the drafting of this grant. There were no drafts in her handwriting, and even Dr. Angelides admitted

that it was he who took the figures to Medical Illustrations for reproduction for the grant, since Dr. Wible was away for Christmas. Tr. at 1535-36. Dr. Angelides's principal argument was that, contrary to ORI's and Dr. Wible's assertions, he could not have written the grant application in the single week Dr. Wible was away, without any input from her whatsoever. Ang. Br. at 49-51. This argument misrepresents the position of ORI and Dr. Wible. Dr. Wible stated that she frequently discussed the project with him, showed him relevant journal articles and her experimental results, and specifically informed him prior to leaving for Christmas of her plans to conduct PCR experiments to overcome the obstacle she had just recently identified. Wible WD at 14-15. The Panel found that Dr. Wible's laboratory notebooks substantiated her testimony that she discovered the need for a change in the experimental protocol just prior to leaving for Christmas, and that she did not begin the PCR experiments until January 1990. Hearing Exs. 6 and 31. The Panel's review of the journal articles cited and of Dr. Wible's notebook disclosed significant overlapping language with the experimental protocols described in the grant applications. See, e.g., Id. at 24, discussing ORI Ex. 13. Dr. Angelides's assertion that the only way this information could have been inserted into the grant was through Dr. Wible's duplicity was not credible.

In addition, the scientists who worked in Dr. Angelides's laboratory all testified that Dr. Angelides was aware of the experiments in his laboratory. See discussion and cites in disulfide bridges section. Thus, Dr. Angelides's claim that he was unaware of the true status of Dr. Wible's experiments, and thought she was enjoying what would have amounted to remarkable successes, was not credible. In addition, Dr. Angelides admitted before the Baylor Sub-Committee that the volume of experiments that he was stating that Dr. Wible had performed was "superhuman." Record Ex. 23, at 247.

In particular, there were several aspects of these complex experiments that Dr. Angelides would have particularly noted. Figures 10/5A and 12/5B contain very specific claims about the yield of the experiments they purport to represent. With regard to the claim that PCR techniques were used to achieve the successes reported in the grant applications, the Panel noted that Dr. Angelides cited with approval Dr. Berget's testimony that PCR was a relatively new technique in 1989, and he stated that his laboratory did not own a PCR machine at the time. Ang. Br. at 69. Thus, it is doubtful that Dr. Angelides was unaware that these experiments had not been done, at least at the time NS24606-05 Deferral was submitted.[55]

Dr. Angelides's scenario for the creation of these false figures is also discredited by his misrepresentation of the record. Dr. Angelides claimed that Ms. Wanda Quezada, the secretary who remembered preparing this specific grant document, testified before the Baylor Sub-

[55]The Baylor Sub-Committee differentiated between NS24606-05 Deferral and GM48816-01 in finding that the claim that PCR experiments had been performed could possibly have been honest error for the latter grant, since by then Dr. Wible had performed such experiments, albeit unsuccessfully. Baylor Report at 81. Dr. Angelides was not charged with misconduct in this regard in the present proceedings.

Committee that Dr. Wible pasted figures into NS24606-05 Deferral. Ang. Br. at 59. However, a close reading of her testimony shows that while Ms. Quezada did remember that Dr. Wible once supplied figures for a grant that Ms. Quezada typed, she did not state that she remembered Dr. Wible pasting figures into NS24606-05 Deferral. Hearing Ex. 21 (10/7/93 Quezada testimony before Baylor Sub-Committee) at 9, 41; Tr. at 1222. In addition, the Panel found that pieces of prior testimony by Dr. Owen Jones, which Dr. Angelides reproduced in his brief but never placed in the record in context, did not at all state, as Dr. Angelides claimed, that Dr. Jones saw Dr. Wible working directly on the grant. Cf. ORI Br. at 46. Consequently, these excerpts, even if accurate, did not contradict Dr. Jones's testimony before the Panel that "I never saw Barbara sit down at a desk, writing with Kim. I never saw Barbara taking figures to Kim or from Kim or doing the kinds of thing that one does during a grant writing." Tr. at 532 (Jones). Moreover, Dr. Angelides attempted to imply that because some students had been shown some grants at some time, it was his practice always to share drafts of grant applications, and therefore he must have shared NS24606-05 Deferral with Dr. Wible. To the contrary, if Dr. Wible had indeed actively participated in drafting this grant application, it would have been a deviation from the normal grant-writing practice of Dr. Angelides. See discussion in section on disulfide bridges project. Consequently, the Panel found that the only evidence in the record that these undisputed falsifications were the responsibility of Dr. Wible was the testimony of Dr. Angelides to that effect.

On the other hand, the Panel found that, in addition to our assessment of Dr. Wible as a highly credible witness, the documentary evidence and the circumstances surrounding this project made it improbable that it was Dr. Wible who was responsible for the falsifications in these grant applications. Although Dr. Angelides claimed that Dr. Wible gave him the finished figures and text for insertion in grant application NS24606-05 Deferral, no draft version of any of the inaccurately labeled figures or text was found in Dr. Wible's laboratory notebook or files. Baylor Report at 81, 101. Furthermore, she left the accurately labeled primary data in her notebook, which remained in Dr. Angelides's laboratory after her June 1991 departure. The Panel determined from its examination of Dr. Wible's original notebooks that they clearly disclosed that the experiments Dr. Wible conducted in furtherance of this project all failed. Hearing Exs. 6 and 31. These failures were recorded in the forms of data, such as scintillation counts, autoradiograms, and gels, that Dr. Angelides could have understood, even without a molecular biology background, since they involved the measurement of products rather than the analysis of molecular biology techniques. If Dr. Wible had indeed given Dr. Angelides false data, one would expect that she would have altered or destroyed the correctly portrayed data in her notebooks to avoid detection. Moreover, by the time she left the notebooks behind, Dr. Angelides had already engaged another molecular biologist to work in his laboratory, Dr. Steven Scherer. Thus, in addition to the danger of Dr. Angelides discovering her fraud by comparing the correct with the incorrect data, there was a serious risk that Dr. Scherer would uncover the fraud if he tried to reproduce her allegedly successful experiments.

The Panel considered the plausibility of the scenario that Dr. Wible gave Dr. Angelides false data before the January 1, 1990 deadline for the NS24606-05 Deferral submission. If such an event

had indeed occurred, then the Panel, concluded, based on the testimony of the witnesses from Dr. Angelides's laboratory that --

(1) Dr. Angelides would surely have expected to hear of the data in his group meetings at least once in the next six months. No laboratory member recalls such a presentation of the sort of results claimed in the deferral, which would have been grounds for a major celebration.

(2) If Dr. Wible had presented such false data with the hope of confirming them later, she would be unlikely to have recorded the attempts to do so in her notebook, since it would provide evidence of her cheating. Instead, Dr. Wible's laboratory notebook contains six months of well-documented failures to achieve even the first steps of this project.

(3) If Dr. Wible had misled Dr. Angelides with false data in December 1989, into believing that the molecular biology part of the project was essentially and successfully completed, then Dr. Angelides would have wanted to involve the rest of the laboratory in bringing this exciting project to conclusion and publication in the shortest possible time. Instead, he allowed Dr. Wible to continue with molecular biology experiments that should not have been necessary, and then did not object when she abruptly dropped the project altogether.

(4) If Dr. Wible had given Dr. Angelides false data in December 1989, some discrepancy between her outrageous claims and the real lack of success shown in her notebooks would certainly have become apparent to even the most detached of principal investigators over the next year and a half. Yet, Dr. Angelides continued to use the false data without noting any discrepancies.

The Panel concluded that, when the scenario that Dr. Angelides proposes is considered in detail, it bears little resemblance to the reality of scientific laboratories conveyed by the scientific witnesses in this case.

As for the GM48816-01 grant application, it is undisputed that Dr. Wible left the Angelides laboratory six months before its submission. As noted above, the textual statements about Figures 5A and 5B differed significantly from those concerning their predecessor figures, which indicates that they were not merely copied from one grant application into the other. As the Panel discussed elsewhere, several experts who testified before us, including some proffered by Dr. Angelides, testified that a principal investigator should discuss with the experimentalist any data presented whose interpretation is open to question. Wilkemeyer WD at 7; Gilbert WD at 34; Tr. at 637 (Pfenninger). Dr. Wible was merely in another laboratory at Baylor at the time, and therefore would have been readily available for Dr. Angelides to consult about her data if there was any confusion.

The Panel also found significant the fact that the falsifications in NS24606-05 Deferral were brought to light because of Dr. Wible. While the Baylor Sub-Committee was questioning her about statements in GM48816-01, Dr. Wible informed them that there was a predecessor grant,

and asked them to look for it. Tr. at 434-35. At that point in the investigation, Dr. Angelides had accused Dr. Wible of scientific misconduct but apparently had not disclosed to the Baylor Sub-Committee the existence of the earlier grant. Id. Since NS24606-05 Deferral was submitted while Dr. Wible was present in the laboratory, rather than after her departure (as was the case with GM48816-01), her disclosure of the existence of that grant, with its additional distortions of her data, lends credibility to her position that she did not know that her data were being seriously misrepresented in submissions to NIH.

In addition, both Dr. Angelides and Dr. Wible acknowledged that at the time grant application NS24606-05 Deferral was submitted, they had an intimate personal relationship. In that context, Dr. Angelides never explained what Dr. Wible's motive would be for giving him false data to put in a grant application that she knew he was signing as principal investigator. While ORI made some general assertions, denied generally by Dr. Angelides, that his laboratory may have been experiencing a funding crisis in late 1989, that point was never fully developed. In any event, Dr. Wible stated that there was never a time during her tenure with Dr. Angelides that she feared the loss of her job due to funding problems. Tr. at 304. Dr. Wible never drafted or submitted to journals any papers claiming success in any of the steps of the project, which was inconsistent with her claiming success to Dr. Angelides. See Tr. at 540 (Jones) ("[If I would have succeeded in such a project] I wouldn't have had a paper. I would have had a Nature paper. I mean, this is a really big deal. It's a very big deal.").

Consequently, the Panel concluded that the preponderance of the evidence in this record indicates that Dr. Angelides was the person responsible for the creation and submission of the falsified figures and text.

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3. Intentionality of the misrepresentation of the data

The Panel next considered whether the preponderance of the evidence supported a conclusion that Dr. Angelides intentionally misrepresented the data. All of the figures at issue were added to grant application NS24606-05 after it was deferred for further information in November 1989. Dr. Angelides did not claim that the misstatements in the figure legends and associated text of NS24606-05 Deferral and succeeding grants occurred by honest error or interpretation of data, but rather that Dr. Wible gave him the figures and text as they appeared in the grant applications, knowing that the falsifications would be submitted to NIH. Ang. R. Br. at 145-49. He argued that he was not knowledgeable enough about molecular biology to be able to recognize from either the unlabeled data that she allegedly gave him (Ang. Br. at 94), or even from the data that the Baylor Sub-Committee and ORI characterized as clearly labeled that her alleged claims of success in the project were false. Id. at 102. Consequently, he maintained that his submission of material that has now been established as false was not intentional.

Since the Panel had Dr. Wible's original notebooks to examine in light of Dr. Angelides's and ORI's arguments, any confusion potentially created by Baylor's or ORI's allegedly selectively presenting or rephotographing data was easily resolved by direct inspection of the primary data.

These were looseleaf binders marked on the spine with, respectively, "9-89 ➜ 12-89, NFL in vitro transcription + translation, NF-Kinase cDNA sequencing, NaCh in vitro translation" (Hearing Ex. 6); and "1/90 - 10/90 - NF Kinase cDNA sequencing, tRNA supp cloning, NaCh expression Vector cloning" (Hearing Ex. 31). Dr. Angelides did not allege, as he did with respect to other experimentalists, that there were any data from Dr. Wible's experiments located anywhere other than these notebooks.

Upon inspection, the Panel found that Dr. Wible's notebooks clearly described the experimental protocols being used and provided the resulting data in an orderly fashion that was not difficult to follow. Moreover, the misrepresentations about these data in the grant applications-- for example, in Figure 8A, calling an enzyme restriction experiment a PCR experiment using cysteine and phenylamine when none of the words "PCR," "cysteine (cys)," or "phenylamine (phe)" appeared anywhere on the page containing both the protocol and the data -- were too flagrant to credit to honest confusion about the experiments. See Record Ex. 1, at Enc. II.C.2.3 (photocopy of relevant page from Hearing Ex. 6.) In fact, Dr. Angelides's alleged confusion about the primary data was of recent vintage; in reviewing them with the Baylor Sub-Committee, Dr. Angelides was able to interpret them well enough to charge Dr. Wible with scientific misconduct. Record Ex. 29. Inasmuch as Dr. Angelides's principal defense was that Dr. Wible gave him the figures and text already assembled and ready for inclusion directly into NS24606-05 Deferral, his assertions before the Panel that the primary data are misleading appeared to be an attempt to distract from the central fact that the four figures and their associated text were patently false.

Dr. Angelides also contended that there was no evidence that the false figures and statements were material to the grant applications, which he contended made it unlikely that the falsifications were intentional on his part. Ang. Br. at 70-76. In particular, he pointed out that PCR was only one method stated in the NS24606-05 Deferral as a means of engineering the suppressor tRNAs so that they had the proper ending. Id. at 76. In addition, he noted that Dr. Berget and Dr. Wible characterized the PCR experiment as merely a preliminary step to establish that the laboratory was capable of succeeding in the project. Id. at 70. He also contended that the TMV experiments were unnecessary since the Murgola genes had already been shown to be functional. Id. at 70-71.

That all of the figures and text the Panel has found to be falsified claimed success in complex experiments and were inserted into the grant application in response to a request for further information about the feasibility of the project shows on its face that the claims were material. Dr. Angelides wrote in the second paragraph of his NS24606-05 Deferral submission, "With respect to experiments to prepare fluorescently modified NaCh proteins, I provide further experimental details, describe what we have accomplished and how we have solved certain problems with the probe mutagenesis approach, and experiments in progress and planned." Record Ex. 11, Att. at 1. In this manner he highlighted the new material, including the falsified experiments. Dr. Angelides also either mischaracterized or ignored Dr. Wible's and Dr. Berget's explanations of the significance of the false claims. While it was true that the grant application

identified as an alternative method to PCR for shortening the suppressor tRNAs the use of overlapping oligonucleotides, by presenting data labeled as PCR results Dr. Angelides expressly claimed in NS24606-05 Deferral that PCR had actually been used and had already been demonstrated to work at a time when the PCR method was a planned rather than a completed experiment. Moreover, he continued to make that claim in succeeding grant applications even after Dr. Wible's PCR experiments had failed and she was attempting to use the alternative method. Wible WD at 30 (Dr. Wible began using alternative methods in May 1990). In addition, while the PCR experiment described in Figure 8C was not per se a step in the project, it was valuable as a step to ascertain whether the proposed methods would work in vitro. Berget WD at 21. In a similar vein, Dr. Angelides's contention that experiments to transform the Murgola genes were not necessary, because they had already been described as functional in suppression and inserting an amino acid into a translated protein (Ang. Br. at 70-71), ignores Dr. Wible's testimony that she could not use the tRNA genes in the plasmid that Dr. Murgola had given her because that plasmid was designed for expression in bacteria rather than in a test tube. Wible WD at 13. The Panel therefore concluded that the falsifications were material to the grant application because they tended to show that Dr. Angelides's laboratory was capable of successfully performing steps to accomplish this admittedly complex and novel project.

In addition, there were significant changes that occurred from NS24606-05 Deferral to GM48816-01 in the figure legends and text. Along with the passage of time -- from December 1989 to January 1992 -- that should have seen further developments in the project, and the departure from his laboratory of the molecular biologist responsible for these experiments, these circumstances make it unlikely that the claims in grant application GM48816-01 were merely the innocent repetition of prior errors.

These factors taken all together -- the attempt to obfuscate the issue of fault by claiming that the data were not clearly labeled when Dr. Angelides had already admitted that they had been misrepresented, the materiality of the claims of success to the feasibility of the project, and the changes and revisions made to the falsified claims in succeeding submissions -- led the Panel to conclude that Dr. Angelides's inclusion of all these falsifications in the grant applications was intentional.

4. Additional Arguments offered by Dr. Angelides on this issue

Dr. Angelides's principal contention regarding the falsified figures was that Dr. Wible gave them to him in the form in which he submitted them to NIH and that he never questioned them. He also implied, however, that he could not have discovered her fraud and, further, that she did not testify truthfully about her experiments, so that the Panel should not believe her testimony that she did not prepare any of the grant applications. Ang. Br. at 119. Since Dr. Angelides did not claim that he had in fact prepared these figures himself from Dr. Wible's data and made honest mistakes as result of difficulties in interpreting her data, Dr. Angelides's allegations about Dr. Wible's notebook are only relevant insofar as they might impugn her credibility. In this

connection, Dr. Angelides contended that Dr. Wible's notebooks did not support her testimony about the progress of her experiments because:

(a) her 1989 notebook contained a reference to a PCR experiment conducted prior to December 1989, which contradicted Dr. Wible's testimony that she did not conduct such an experiment before January 1990[56] (Id. at 68);

(b) her 1989 notebook contained an experiment dated December 13, 1989 with TMV (tobacco mosaic virus) to translate the suppressor tRNAs, which rebutted her assertion that the suppressor tRNAs had not been generated at that time, because it would not made sense to do an experiment with the tRNAs if they were useless reagents (Id. at 56, 103);

(c) there was evidence in her 1990 notebook that contradicted her assertion that she was never successful with her 1990 PCR experiments in shortening the suppressor tRNAs by the requisite two nucleotides (Id. at 80);

(d) the notebooks were misleading because Dr. Wible used terms such as "PCR" and "aminoacylate," terms indicative of completion of those processes, when she testified that she actually meant "attempt to use PCR" and "attempt to aminoacylate" (Id. at 7); and

(e) since Dr. Wible did not provide an interpretation of her experimental results within her notebooks, it was impossible to tell if her experiments indeed failed (Id. at 94, 102).

Since Dr. Angelides agrees that the primary data were misrepresented in all the subject figures, and we have already concluded above that Dr. Angelides was responsible for the false presentation of these data in this grant, Dr. Angelides's assertions, even if true, would not ameliorate his conduct. Furthermore, the Panel found Dr. Wible's testimony credible in its delivery and consistent with the other facts in the record. Dr. Wible's notebooks were submitted as Hearing Exhibits 6 and 31, and thus were readily available for us to conduct a thorough review of the notebooks' contents in light of Dr. Angelides's claims. The Panel found that the notebooks were completely consistent with the testimony challenged by Dr. Angelides. Our specific findings on each of Dr. Angelides's attacks on Dr. Wible's credibility are discussed below.

(a) The Panel determined that the PCR experiment, referred to by Dr. Angelides as contradicting Dr. Wible's testimony about when she began PCR experiments, was conducted in November 1989 and had nothing about it to even remotely suggest that it involved the fluorescent amino

[56]Dr. Angelides argued that during her testimony before the Panel, Dr. Wible admitted that a December 14, 1989 experiment recorded in her notebook was a PCR experiment. The Panel reviewed the cited testimony and found no such admission. Tr. at 423-25.

acid project.[57] Hearing Ex. 6 at first page dated Nov. 16, 1989. We also found that Dr. Wible's statement about not having conducted PCR experiments prior to December 1989 clearly referred in context to the project to incorporate fluorescent amino acids. Wible WD at 26. In addition, Dr. Wible indicated that she did not obtain the suppressor tRNA clones for the project from Dr. Murgola until early December 1989, and thus she could not have done the relevant PCR experiment before then. Id. at 13.[58]

(b) Dr. Angelides contended that it was illogical for Dr. Wible to use the suppressor tRNAs in her December 13, 1989 experiment, if they were not functional, and alleged that she failed to explain this discrepancy. This argument is spurious. Dr. Wible explained in her written direct testimony that the purpose of the TMV experiment was precisely to determine whether the suppressor tRNAs were functional, and she indicated that the autoradiogram showing her results demonstrated that they were not:

> Question: "How would this experiment have been successful?
> Answer: "If the transcribed cys-suppressor tRNA had suppressed the stop codon, the top protein band would have become darker or the relative intensities of the two

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[57]Dr. Angelides also made an argument that photocopies of laboratory notebook pages of the experiments whose data are misrepresented in Figure 8C and 12, were not found in the GM48816-01 file when it was confiscated by the Baylor Sub-Committee but were placed there by the Sub-Committee when he provided these pages prior to his November 1993 appearance before the Baylor Sub-Committee. Ang. Br. at 60-61, 66, 74-75. He argued that the corresponding Enclosures had post-it notes with his handwriting photocopied on them while the original laboratory notebook pages contained no such notes. The Panel found that the photocopy of Record Exhibit 1, Enclosure II.C.2.3, the copy of the data used in Figure 8C, is an exact copy of the laboratory notebook page. Dr. Angelides discussed this page in detail with the Baylor Sub-Committee during his September 1993 appearance before them and no one mentioned a post-it on the page at that time. Record Ex. 19, at 428-433. Moreover, he agreed that he was given this page at the time he was writing the NS24606-05 Deferral grant application. Id. The Panel found two copies of the relevant page of data used in Figure 12 at Record Exhibit 1, Enclosure II.C.2.4, one with a post-it apparently photocopied on the original and one an exact copy of the original. Dr. Angelides discussed the page with the post-it on it during his November 1993 appearance and testified that it was among the photocopies given to him by Dr. Wible during December 1989 or early 1990. Record Ex. 23, at 164.

[58] Dr. Angelides also argued that the oligonucleotide records introduced by ORI in support of Dr. Wible's testimony that she did not even order the oligonucleotides needed until January 1990 were insufficient to establish that point. Ang. Br. at 68-69. Since Dr. Angelides also indicated that such oligonucleotides were commercially available at the time, however, and since the Panel's review of Dr. Wible's laboratory notebook confirmed her testimony about the timing and results of these experiments, the Panel did not find it necessary to trace the source of the oligonucleotides used in them.

> largest proteins would have changed. However, it did not. The stop codon was not suppressed more efficiently, instead much less protein was synthesized."

Id. at 43. Dr. Wible also testified that she discussed this experiment at the time with Dr. Angelides. Id. at 43. Dr. Wible's explanation was confirmed by Dr. Berget in her written direct testimony. Berget WD at 36-37. These written testimonies were part of the hearing, and were made available prior to Dr. Wible's in-person appearance for cross-examination. However, although Dr. Angelides's counsel asked Dr. Wible some questions during cross-examination about this experiment, he never questioned her to elicit the explanation that Dr. Angelides contended later she should have supplied. See Tr. at 414-17.

(c) Dr. Angelides did not point to any specific PCR experiment in the 1990 notebook that he claimed was successful. The Panel reviewed the notebook and found that it confirmed Dr. Wible's testimony that she made repeated attempts to produce the truncated tRNAs by PCR beginning in January 1990, but she was never successful.[59] For example, on the notes of an experiment that she conducted January 30, 1990, she wrote "no bands in correct size range." Hearing Ex. 31 at fourth page for experiment dated 1/30/90. Moreover, Dr. Angelides did not explain why, if she was successful, she repeated the experiment numerous times (on equipment in another scientist's laboratory) rather than proceeding to the next step.

(d) The Panel concluded that Dr. Wible's interpretation of her use of terms like "PCR" or "aminoacylate" as shorthand for reporting the methods she was using to accomplish her objectives was reasonable and credible. Tr. at 481-82. In the context of her notebook, the Panel found no implied assertion of successful results. Furthermore, her terminology could not have been misleading, since the displayed data always demonstrated whether those objectives were accomplished.

(e) The Panel agreed that Dr. Wible's notebooks contained only few instances where there was a specific summary statement that an experiment did not work. However, Dr. Angelides produced no expert testimony that such a summary was required or was an accepted standard for reporting data, and the display of data following each experimental protocol clearly indicated the results. In addition, as noted above, that the same experiments were shown as done repeatedly

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[59]Dr. Angelides cited to testimony by Dr. Scherer as establishing that Dr. Wible had given him "the suppressor tRNA clones she had created," when she left the Angelides laboratory. Ang. Br. at 80, citing Tr. at 1195. The specific testimony was, "Question: Do you recall whether Dr. Wible in this short transitional process, provided you with the tRNA suppressor clone? Answer: Yeah. She showed me where they were, and she gave me notes based on that project. But I never touched it." The Panel did not find this testimony established that Dr. Wible was lying about her lack of success in the project. The tRNA suppressor clone which Dr. Scherer recalled having been left with him may have simply been the Murgola tRNA suppressor clones with which Dr. Wible had been unsuccessfully trying to work. This would be consistent with the evidence in her laboratory notebooks that she had had no success.

rather than as part of an orderly progression in this multistage project, was also a clear indication of their failure.

5. Conclusion on the figures in applications NS24606-05 Deferral and GM48816-01

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the inclusion of Figures 8C, 10, 11 and 12 in NS24606-05 Deferral and Figures 5A and 5B in GM48816-01. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides acted intentionally to misrepresent the data in the figure legends and associated text. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive, and the conduct proven constituted scientific misconduct.

D. <u>False statements about research progress in the unillustrated textual claims in NS24606-05 Deferral, GM48816-01, and the two continuing applications for NS01218</u>

As noted above, Dr. Wible testified that she was unsuccessful in her attempts to use PCR to generate suppressor tRNAs that had the last two nucleotides deleted to allow them to be proper substrates for the chemical addition of the fluorescent amino acids. After attempting these experiments from January through May 1990, she tried a different method, using overlapping synthetic oligonucleotides to produce tRNAs with the correct ending, but she was unsuccessful in these efforts as well. Wible WD at 30-31, 49. Around June 1990, she testified that she abandoned these efforts and moved on to other projects until she left the Angelides laboratory in July 1991. <u>Id.</u> at 61. As the Panel previously stated, we reviewed Dr. Wible's notebooks for September 1989 through October 1990 and found that her testimony was well-documented. Thus, the Panel determined that Dr. Wible was accurate when she testified that the fluorescent amino acid project did not proceed to the stage where the Angelides laboratory was able to attach fluorescent amino acids to the suppressor tRNAs through aminoacylation.

The Baylor Sub-Committee and ORI both identified certain statements in four grants, apart from the text associated with the falsified figures, that they concluded were false claims of success in this project. Dr. Angelides contended before the Panel that two of these statements, which appeared in grants NS24606-05 Deferral and GM48816-01, were not false because he had in fact performed the organic chemistry experiments described there himself. Tr. at 1545. He maintained that the other two statements, which appeared in grants NS01218-04 and -05, were also not false because they were being misinterpreted as claims that the project was successfully completed rather than as reports of preliminary experiments that had actually occurred. Ang. Br. at 53-54. He also contended that these statements reflected Dr. Wible's reports to him on the progress of the project. <u>Id</u>. Below the Panel first reviews the statements in the competitive grants about the organic chemistry experiments and considers the evidence offered by both sides as to whether these statements are false. If either or both are false, we need not resolve the question of who is responsible for their inclusion in these grants, since Dr. Angelides apparently admits authorship, but we must resolve the question of the intentionality of the falsification so as

to determine whether such false statements constitute scientific misconduct. Next, we review the second set of statements in the NS01218 grants and consider whose interpretation of their meaning is correct. If we agree with ORI that the statements claim success, our determination above that Dr. Wible did not succeed in her experiments and that Dr. Angelides intentionally misrepresented the results of her experiments means that these statements are false and constitute scientific misconduct.

1. The organic chemistry experiments

The first allegedly false statement at issue is found in the NS24606-05 Deferral grant application, where Dr. Angelides stated --

> In small scale pilot reactions with S-anthraniloyl or coumarin á-N-carbobenzyloxy carbonyl cysteine deprotection with H_2/Pd has given a yield of 48%. We are in the process of purifying the products by HPLC on C_{18} reverse phase column and characterizing these products by mass spectrometry and NMR.

Record Ex. 11, at 16. According to ORI, this statement is false because it claims ongoing purification by HPLC and the evidence showed that Dr. Angelides did not perform these experiments. ORI Findings at ¶¶ 262-265.

In addition, the GM48816-01 grant application stated --

> In reactions with S-anthraniloyl or coumarin *á-N-carbobenzyloxy* carbonyl cysteine deprotection with H_2/Pd we have gotten yields of 48%. We have purified the products by HPLC on C_{18} reverse phase column and characterizing these products by mass spectrometry. The N-á-carbobenzyloxy (sic) protected amino acids are then acylated by carbonyldimidazole coupling to the 2'(3') 0 pCpA. The deprotected pCpA-fluorescent amino acid is then ligated directly to the $tRNA^{Cys}_{CUA}$ missing the 3' CA with T4 ligase which has a broad specificity for the amino acid group. We have had typical yields of 40%; from 1 mg of in vitro transcribed tRNA, we obtained 400 mg of fluorescently misacylated suppressor tRNA.

Record Ex. 13, at 22. ORI contended that this statement was false because, as indicated above, Dr. Angelides did not purify products with HPLC and, consequently, the experiments and yields described in the rest of the passage could not have been accomplished. ORI Findings at ¶¶ 262-265; 267-268.

According to ORI, the evidence also demonstrated that both these statements were false because the described pCpA-fluorescent amino acid was never linked directly to $tRNA^{Cys}_{CUA}$ missing the 3' CA with T4 ligase. ORI maintained that there were no primary data showing that the HPLC experiments were performed, no primary data or other records showing that the dinucleotide pCpA was ever purchased or produced by Dr. Angelides's laboratory or that it was linked to the

fluorescent amino acids, and there were no primary data or records showing the ligation of the allegedly linked pCpA-fluorescent amino acid to the suppressor tRNA. ORI Br. at 54-55.

Dr. Angelides testified that he himself performed the chemical reactions described in these two grant applications, since it was within his expertise as an organic chemist. Tr. at 1545-46. He had admitted before the Baylor Sub-Committee that no record of these experiments appeared in his laboratory notebook (Record Ex. 23, at 47), but he contended before the Panel that he had made notes that were placed in a manilla folder that must have been confiscated and subsequently lost by Baylor. Tr. at 1545-46.[60] In his brief, Dr. Angelides contended that ORI's charges rested on Dr. Berget's inexpert testimony which was "obviously confused" about the chemistry involved. Ang. Br. at 113. Thus, he contended, the statement in GM48816-01 that the pCpA- fluorescent amino acids had been ligated to the suppressor tRNAs was not false. Id. With respect to the language in the grants about the HPLC part of the experiments, Dr. Angelides's position was that his laboratory was in the process of using HPLC for separation, and that ORI did not show that Dr. Angelides was not in the process of characterizing the derivatives using these methods for NS24606-05 Deferral or that, by the time GM48816-01 was submitted in 1992, the products had not been purified by HPLC. Ang. Br. at 115-16. In addition, Dr. Angelides stated that he could have run the HPLC machine himself. Further, Dr. Angelides argued that the lack of any HPLC data should be held against Baylor, not him. Id.

The Panel reviewed these charges and concluded that the clear language of the text does claim that particular experiments were performed, including specific product yields, that should have produced primary data in the form of HPLC profiles, oligonucleotide orders, and laboratory notebooks or other records of experimental protocols. As Dr. Angelides submitted no primary data whatsoever, the sole evidence that these experiments were ever undertaken was Dr. Angelides's testimony. This testimony has shifted and changed constantly since Baylor first identified this issue, and the Panel found that these dramatic shifts destroyed Dr. Angelides's credibility. We therefore conclude that the preponderance of the evidence indicates that the statements are false. We highlight the principal reversals and revisions in position below.

Dr. Angelides's testimony about any notes he made about these experiments varied. Before the Baylor Sub-Committee, he stated that the reactions were so easily accomplished that he did not need to write out any protocols or make any notes. Record Ex. 23, at 47. He said that he gave the product to Dr. Wible for her experiments; she denied receiving it. Id. at 55-56. Only at the hearing before this Panel did Dr. Angelides state for the first time that he specifically remembered doing these experiments, but that he used CpA rather than pCpA as he had told the Baylor Sub-Committee. Tr. at 1545-46. Dr. Angelides stated that his notes for this process were placed in a manilla folder that he presumed was confiscated by Baylor. Id. No such folder was found by the Baylor Sub-Committee.

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[60]The Panel noted that if this was Dr. Angelides's routine method for keeping his own scientific records, he must take full responsibility for any lapses of notebook organization by his junior colleagues.

As indicated elsewhere, the Panel has determined that Dr. Angelides's claim of spoliation of the record in general is unsupported. In this instance, Dr. Angelides's initial recollection of whether notes existed at all was shaky, then his account of how the experiments were conducted was hazy, until finally, some eight or nine years after the experiments, he suddenly remembered that he had synthesized a needed reagent using a complicated procedure. When combined with the fact that he claimed that the experiments resulted in a specific quantity of product that he gave to another scientist who denied ever receiving it, and with the fact that no other records that would have been generated as part of the process (gels, oligonucleotide vouchers or invoices, pCpA or CpA purchase records) have been provided, the Panel concluded that it is most likely that no experimental notes ever existed to be lost or spoiled.

In addition, Dr. Angelides's shift in position on the manner in which he obtained the necessary pCpA for the experiments was noteworthy. Before the Baylor Sub-Committee, Dr. Angelides maintained that Dr. Wible gave him the pCpA since it was a molecular biology reagent. Record Ex. 23, at 57. Dr. Wible denied this. Id. at 58. After the Baylor Sub-Committee reported that not only had Dr. Wible denied supplying the pCpA but that the Sub-Committee could find no commercial vendor who sold it, Dr. Angelides testified before the Panel that it was CpA that Dr. Wible gave him, to which he was able to add the necessary phosphate. Tr. at 1545. Even later in the proceeding, apparently in response to Dr. Berget's testimony that CpA was not commercially available in 1989 either (Tr. at 167), Dr. Angelides contended that CpA could be prepared using any commercial oligonucleotide synthesizer. Ang. Br. at 113. It is noteworthy that Dr. Angelides did not espouse these positions in his response to the Baylor Report, but waited until his appearance before the Panel. These belated shifts in claimed experimental protocol seemed to the Panel an effort by Dr. Angelides to inject "confusion" as to his purported use of CpA or pCpA, rather than evidence of any confusion or lack of expertise on the part of Dr. Berget, as Dr. Angelides claimed. The Panel also noted that although the complete oligonucleotide log book for 1989 through the beginning of 1992 was submitted as part of this record at Dr. Angelides's request (Panel Ex. 13), Dr. Angelides has not cited to anything in that book to support his claim that the facility was used to prepare CpA. See also Letter from ORI to the Panel (Nov. 9, 1998), and Att. 2 (submitting and authenticating Panel Ex. 13). Dr. Angelides also has not produced any receipts or correspondence to show his purchase of CpA from any commercial source. The Panel thus found that Dr. Angelides's testimony concerning his production of pCpA linked fluorescent amino acids using CpA is not credible.

The Panel's conclusion concerning the credibility of Dr. Angelides's assertion that these experiments were actually performed is further buttressed by his evolving account of the HPLC part of the project, which also changed dramatically. Dr. Angelides testified before the Baylor Sub-Committee that he would have required assistance to operate the HPLC machine, and he named the individuals in his laboratory who would have provided such help. Record Ex. 23, at 48-49. The Baylor Sub-Committee interviewed all those named and reported that it was unable to locate anyone in Dr. Angelides's laboratory who remembered helping him perform the necessary HPLC for this project or saw him working with the HPLC or at the bench in December 1989, prior to the submission of NS24606-05 Deferral. Baylor Report at 95, 100. Subsequently,

Dr. Angelides testified before the Panel that he had determined from a review of his records that he actually had done some HPLC, although he never expressly stated that he remembered employing it for this particular project: "With respect to the HPLCs, I can't be absolutely certain at this time, but I believe that I possessed the necessary expertise to be able to do the HPLCs at that time with assistance of somebody in the laboratory." Tr. at 1544. This recollection did not include naming who assisted him, and, as noted above, no one who was in the laboratory at the pertinent time remembered doing so. Dr. Angelides never provided records or notes from these specific HPLC experiments. However, he argued that "there are indeed records that indicate that Dr. Angelides did himself perform HPLC to purify various compounds." Ang. Br. at 116.[61] The record that Dr. Angelides claims supports his position is an entry in the mass spectrometry log book indicating that, on November 9, 1990, Dr. Angelides submitted samples from an HPLC fraction and, on November 20, 1990, he asked for a full scan on a "daughter," which he claimed was consistent with synthesis of a small organic molecule during this time. Id. at 116-17. Dr. Angelides did not explain why he waited until his brief to make this claim, when the existence of these experiments has been in doubt since 1993. In any event, the references were too vague to establish that he did the challenged experiments, and the dates identified are well past the submission date of NS24606-05 Deferral. Given the timing of the introduction of this document, its lack of specificity, and the lack of credibility of the party proferring it, this document does not provide a basis for the Panel to conclude that the HPLCs were performed at the time that Dr. Angelides claimed that they were done in his grant submissions.

The Panel found no documentary evidence (primary data or otherwise) that supports Dr. Angelides's claim that these experiments were done, and found Dr. Angelides's testimony on this topic lacking in credibility because it has been inconsistent with his past testimony and with the testimony of all other witnesses who might have personal knowledge of this matter. Consequently, the Panel concluded that the preponderance of the evidence establishes that the statements are false.

Having concluded that the statements are false, in order to determine whether they constitute scientific misconduct, the Panel must consider who is responsible for their inclusion in these competitive grant applications and whether the inclusion of the false material was intentional. With respect to responsibility, unlike his defenses with regard to other parts of these grant applications, Dr. Angelides did not claim that another scientist furnished these false statements to him. Instead, he contended that the information stated about the chemical syntheses and HPLCs was in fact correct because he had performed them himself. Tr. at 1544-46. Since the Panel found that these statements were false, and Dr. Angelides had to know that these claims were

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[61]Dr. Angelides also argued that ORI's case failed because Dr. Berget has not provided any review of records to suggest that relevant HPLCs or description of experiments are not contained therein. Ang. Br. at 116. This argument is incorrect, since Dr. Berget testified that the Baylor Sub-Committee was unable to locate any records relating to these experiments in its review of records from Dr. Angelides's laboratory. Berget WD at 45.

false, we therefore found that he was responsible for including the claims that pCpA was linked to fluorescent amino acids and the derivatized compounds were purified by HPLC.

Regarding intentionality, Dr. Angelides argued that ORI provided no proof that his incorporation of this or the other challenged textual statements was intended to respond to specific reviewer comments, other than those that he clearly highlighted on measurement of the fluorescent spectra. Ang. Br. at 120. Dr. Angelides rejected the suggestion, made by Dr. Berget, that these statements addressed the reviewers' concerns about feasibility of the project. Id. at 120, n.102. The Panel has previously stated why it rejected Dr. Angelides's attempts to create a standard of materiality for a false statement that would require that the statement be proven to be responsive to reviewers' comments. Moreover, with respect to the NS24606-05 Deferral grant application, it is evident that this standard was met, since the reviewers' comments that Dr. Angelides listed as addressed in the document included, "the feasibility of one approach to generate fluorescent NaChs I described using a molecular biology method, [and] . . . whether this method will provide active NaChs and adequate protein to carry out the fluorescence measurements I proposed." Record Ex. 11, at Att. p. 1. Certainly, claims that key pilot experiments had been accomplished and specific product yields had been achieved responded to those perceived concerns. In addition, the false statements are clearly material since they claim success in completing a highly sophisticated set of experiments, thereby demonstrating the laboratory's capability as well as the feasibility of the proposed research. Finally, the claims of success in these two grant applications changed significantly and unquestionably escalated. These factors all lead the Panel to conclude that the false statements were intentionally included to improve the likelihood that these two grant applications would be funded.

2. The noncompetitive grant claims

The NS01218-04 continuing career grant application stated --

> Using a series of suppressor tRNAs that we have engineered by PCR with 3'CA ends deleted and that have been chemically charged with fluorescent and phosphoamino acids, we have mutagenized defined regions of a transport protein and the á subunit of AchR [acetylcholine receptor] (with hopes of doing the same experiments with the rat brain NaCh) with an amber suppressor codon (UAG) to incorporate an unnatural amino acid into a unique position of the protein. We have successfully translated the protein in microsomes and measured fluorescent spectra and ^{32}P levels.

Record Ex. 4, at 8. A similar statement was made in the NS01218-05 continuing career grant application, which stated --

> Using a series of suppressor tRNAs that we have synthetically engineered with 3'CA ends deleted and that have been chemically charged with fluorescent and phosphoamino acids, we have mutagenized defined regions of a transport protein,

> the á subunit of AchR; and the rat brain NaCh III with an amber suppressor codon (UAG) to incorporate an unnatural amino acid into the unique position of these proteins. We have successfully translated the protein in microsomes and measured fluorescent spectra and ^{32}P levels.

Record Ex. 5, at 7-8. These two latter statements claim that the project had been completed successfully through step 6.

ORI charged that these statements were false because there is no evidence that natural amino acids were replaced in fluorescent derivatives in a transport protein, AchR and NaChIII. ORI Findings at ¶¶ 272-276. Since Dr. Wible's testimony and laboratory notebooks demonstrate that she was never able to successfully modifiy the suppressor tRNAs to enable her to charge them, no such experiments as claimed in these statements could have been performed. ORI Br. at 52-53.

In response to this charge, Dr. Angelides made three arguments. First, he contended that the statements were being misinterpreted as claiming successful incorporation of the amino acids into the named proteins when they did not mean that. Ang. Br. at 109-11. Second, he contended Dr. Brown's signature as sponsor on these noncompetitive grants implied that Dr. Brown vouched for the stated progress as being true. Id. at 112. (This latter defense reflected Dr. Angelides's earlier position in his Response to the Baylor Report that Dr. Wible must have claimed success in these experiments to Dr. Brown.) Third, Dr. Angelides contended that he based these statements on Dr. Wible's reports of her experiments to him. Tr. at 1547. The Panel reviewed each of Dr. Angelides's defenses in turn.

Dr. Angelides did not challenge the Baylor Sub-Committee's interpretation of these passages in his Response to its Report. Nevertheless, Dr. Angelides testified before the Panel that he did not mean to claim in these statements that unnatural amino acids had actually been incorporated into the proteins. Specifically, he stated:

> The experiments that were detailed there or in these NS01218-04 and 05 were that protein had been translated in microsomes, and we had carried out pilot fluorescence measurements, spectra, to show that we could record spectra from proteins not that the fluorescence group was directly attached to, but in fact that protein that had been translated in a microsome together with a fluorescent group, and that's to say that we wanted to know whether the fluorescent group and the fluorescence could be visualized, that is a signal could be visualized over the background of the microsomes that were being used to translate the protein. There is no statement in which [I] claimed that the fluorescent amino acid was directly attached to either the glucose transporter or the acetylcholine receptor. Fluorescent spectra were measured with a fluorophore in solutions of microsomes that had in vitro translated, and there were pilot experiments.

Tr. at 1548. ORI challenged Dr. Angelides's interpretation of this language and maintained that, even if accepted, there was no evidence showing the performance of even the experiments that Dr. Angelides claimed this language properly reported. ORI Reply Br. at 24-25.

The Panel examined for itself the statements in NS01218-04 and -05 that "[u]sing a series of suppressor tRNAs . . . that have been chemically charged with fluorescent and phosphoamino acids, we have mutagenized defined regions [of specific proteins]. . . with an amber suppressor codon (UAG) to incorporate an unnatural amino acid into a unique position of the protein." Record Ex. 4, at 8; Record Ex. 5, at 7-8. The Panel found that the language, in context, clearly states that the unnatural amino acid was incorporated into the protein. The Panel concluded that his sentence cannot be reasonably interpreted (as Dr. Angelides claimed) as saying that experiments were done to measure the fluorescence signal in proteins translated in microsomes with fluorescent amino acid derivatives that were not necessarily inserted at a specific site by use of modified suppressor tRNAs. The Panel also interpreted the second sentence, "We have successfully translated the protein in microsomes and measured fluorescence spectra and ^{32}P levels," as stating that proteins with the unnatural amino acids incorporated were produced, since the product of a successful translation is the production of a protein whose amino acids correspond to the component RNAs (in this case RNAs that had been engineered to incorporate unnatural amino acids). Thus, we rejected Dr. Angelides's eleventh- hour attempt to render these statements ambiguous. Moreover, we agreed with ORI that the record does not contain, nor did Dr. Angelides provide, any data showing that the experiments that he said these statements reported were performed.

As for Dr. Angelides's defense that Dr. Brown signed these grants as sponsor, and thus must have believed from his contacts with Dr. Wible, who was working in Dr. Brown's laboratory by the time NS01219-05 was signed, that these successes had been achieved, we note that Dr. Brown was not presented as a witness by Dr. Angelides. Consequently, we have no evidence in the record to interpret the basis or meaning of his signature. As discussed in relation to the sponsor's statement on disulfide bridges, this Panel is not reviewing the conduct of Dr. Brown to determine whether he made appropriate efforts to verify the progress which he confirmed as sponsor. Regardless, Dr. Brown's signature does not relieve Dr. Angelides from the responsibility of reporting accurately the state of work in his own laboratory.

With respect to Dr. Angelides's claim that he was only reporting what Dr. Wible had told him about the progress of the project, Dr. Angelides stated that she had communicated to him that "she had mutagenized the acetylcholine receptor, the sodium channel and a transport protein." Tr. at 1547. He argued that the challenged statements in the grants simply reported that these proteins had been translated in the presence of fluorescent derivatives as a pilot experiment in measuring spectra. The Panel above rejected this interpretation of the language of the grants. Furthermore, Dr. Wible denied ever having made even these more limited claims to Dr. Angelides. Thus, she testified, "I never did site-directed mutagenesis of any protein, including the glucose transporter protein or the acetylcholine receptor. Since I never introduced the stop codon into cDNAs, no fluorescent amino acids could have been incorporated into them." Wible

WD at 68. She testified that she never told Dr. Angelides that she had accomplished any of the experiments described. Id. at 70. The Panel did not find credible Dr. Angelides's assertion that he based the statements in the grants on claims to him from Dr. Wible that these experiments had been accomplished. The Panel therefore concluded that Dr. Angelides was responsible for these false claims of experiments that were never conducted.

Since the Panel concluded that the statements are false and that Dr. Angelides is responsible for making them, we next considered whether the making of such false statements was intentional. The Panel found Dr. Angelides's duplication of defenses -- that the claim was not false and that the claim was false because Dr. Wible lied to Dr. Angelides -- troubling, since it suggested an improbable and an implausible scenario: Dr. Wible presented false data; Dr. Angelides wrote a paragraph that only coincidentally sounded as if it was using these false data; however, if read appropriately, the paragraph could describe experiments that were in fact done. While alternative pleading is a regular occurrence in legal briefing, the circuitousness of this complex defense lessens the Panel's confidence in the trustworthiness of Dr. Angelides's arguments in general.

As career grant renewal applications are not reviewed in the same manner as competitive grant applications, and the claims therein may have less direct impact on funding decisions, it can be reasonably argued that false claims in such renewals do not have the gravity of identical claims in competitive grant applications or resubmissions. However, these falsifications nevertheless affected the Panel's overall conclusions concerning Dr. Angelides's conduct regarding this project because they show a pattern of behavior, illustrating that errors were not made on one particularly unfortunate occasion but were the norm. In addition, they illustrate how the claims grew from year to year and so were not due to the propagation of a single error through several applications.

E. Overall Conclusion on Fluorescent Amino Acid Project

The Panel found that the themes observed in other projects continued with this project. Clearly labeled data were presented by Dr. Angelides to support claims of success in experiments that were either unsuccessful or had never been attempted. When the clearly false figures were uncovered, Dr. Angelides tried to deflect responsibility for the falsifications by claiming that he had obtained all the falsified figures and text from another scientist in his laboratory. As the evidence mounted, Dr. Angelides shifted his account of how the data were produced. The experimental results claimed were significant, yet Dr. Angelides attempted to minimize their importance in an effort to downplay the seriousness of making such claims in support of applications for federal funds. Despite Dr. Angelides's efforts to dilute the issues or misdirect the Panel's attention, we concluded that the preponderance of the evidence demonstrated that Dr. Angelides was responsible for these falsifications, that they were intentional, and that all the charges established in the record met the standard for scientific misconduct.

IV. Anti-sodium channel antibodies project

A. Introduction on the anti-sodium channel antibodies project

As previously discussed, much of the focus of the research in Dr. Angelides's laboratory during the period in which the charges here arose was on elucidating the distribution and function of sodium channel proteins. See Elmer WD at 11-12; Gilbert WD at 20. The sodium channel is a large glycoprotein composed of several subunits, the largest of which, the "alpha" (á) subunit, has a molecular weight of approximately 260 kDa. Id. Dr. Angelides, along with other researchers in the field, sought to develop tools to identify and locate sodium channels in different tissues. Id. To this end, one project of the laboratory was to raise antibodies that would specifically detect the á subunit of the sodium channel. During 1987 and 1988, Dr. Elmer was the main experimentalist on this project. At that time, another laboratory (that of Dr. William Catterall) had developed antibodies that recognized sodium channel proteins in central nervous system tissues. Elmer WD at 12; ORI Exs. 11A and 11B. Dr. Angelides's laboratory sought to develop polyclonal and monoclonal antibodies that would detect the á subunit of the sodium channel in both central nervous system (CNS) and peripheral nervous system (PNS) tissue. Elmer WD at 12.

For this purpose, Dr. Elmer developed one polyclonal antibody (named 7493 after the number of the rabbit from the sera of which it was produced) and two monoclonal antibodies (named mAb1 and mAb3). Elmer WD at 12-14; Hearing Ex. 25 (Elmer's thesis at Chapter 5). In order to ascertain whether the antibodies reacted specifically with the á subunit, and not with other antigenic contaminants, Dr. Elmer conducted Western immunoblots against proteins from different tissues looking for reactivity to a protein of the relevant molecular weight, i.e., 260 kDa. Elmer WD at 13; see Hearing Exs. 14, 15 and 51. The monoclonal antibodies produced a single band at the expected molecular weight with crude glycoproteins from rat brain and with purified sodium channel proteins. Elmer WD at 15. However, the polyclonal 7493 antibody reacted strongly with an unknown protein of 170-180 kDa in crude glycoprotein extracts, as well as showing multiple other bands. Elmer WD at 15; see, e.g., Record Ex. 1, at II.C.4.41. Dr. Elmer believed that this protein might be a breakdown product degraded from the large sodium channel protein. Elmer WD at 16-17. After consultation with another laboratory, Dr. Elmer adopted a protease inhibitor cocktail in his preparations to reduce degradation and thereafter the major band shifted up to 260 kDa, although minor bands persisted at the 170-180 kDa range. Id.

Dr. Angelides is alleged to have falsified data and misrepresented experimental results in a number of publications which reported the characterization and use of the 7493 antibody. Below, we discuss first the charges relating to publications in which Dr. Angelides collaborated with several scientists at Yale College of Medicine who used the 7493 antibody in their research. Then, we discuss the charges relating to the publication in Brain Research of a paper describing the characterization of the 7493 antibody in CNS and PNS tissues. In addition, Dr. Angelides is alleged to have falsified data and misrepresented experimental results in the same project in three grant applications that he submitted to seek NIH funding. We discuss the charges relating to the grant applications after our discussion of the publications.

B. The Yale papers

Dr. Angelides collaborated on four papers with Drs. Waxman, Black and others at Yale University School of Medicine. The Yale researchers used the polyclonal antibody 7493 developed by Dr. Elmer in Dr. Angelides's laboratory for immunostaining experiments in rat optic and sciatic nerve tissue. The monoclonal antibodies did not immunostain robustly enough to be useful for this purpose. Black WD at 7. In order to establish the ability of 7493 to recognize specifically sodium channel in the target nerve tissue, Dr. Angelides provided a figure for each paper. Black WD at 9; Waxman WD at 13. The first paper using 7493 in optic nerve was entitled, "Immuno-ultrastructural localization of sodium channels at nodes of Ranvier and perinodal astrocytes in rat optic nerve." 238 Proceedings of the Royal Society 39-51 (1989), Record Ex. 1, at Enc. II.C.4.23 (PRSL paper). Dr. Angelides and Dr. Elmer were listed as co-authors along with three scientists from Yale University School of Medicine. A second paper dealing with optic nerve was published in 1991. "Membrane-Associated Sodium Channels and Cytoplasmic Precursors in Glial Cells," 633 Annals of the New York Academy of Sciences 255-71 (1991), Record Ex. 1, at Enc. II.C.4.24 (ANYAS paper). Dr. Angelides was the only co-author from his laboratory on that paper and so accepted responsibility for its content.

A third paper relating to the use of the 7493 antibody for localization of sodium channels within rat optic nerve was also published in 1989. "Sodium Channels in Astrocytes of Rat Optic Nerve In Situ: Immuno-Electron Microscopic Studies," 2 Glia 353-69 (1989), Record Ex. 1, at Enc. II.C.4.18 (Glia paper). Dr. Angelides and Dr. Elmer were again listed as co-authors. The fourth paper at issue resulting from Dr. Angelides's collaboration with the Yale scientists dealt with studying sodium channel localization in Schwann cells using the 7493 antibody, which was represented as having demonstrated specificity for the sodium channel protein in rat sciatic nerve. "Sodium channels in the cytoplasm of Schwann cells," 87 Proceedings of Nat'l Acad. of Sciences 9290-94 (1990), Record Ex. 1, at Enc. II.C.4.9 (PNAS paper). Dr. Angelides was again the sole co-author from his laboratory on the PNAS paper, and so accepted responsibility for its content.

ORI charged that a figure in each paper contained data that was falsely represented in the corresponding legend and text. ORI further charged that Dr. Angelides was the person primarily responsible for the presentation of the data in each of these papers and that the data as presented were intentionally falsified. Because the alleged falsifications in the PRSL and ANYAS papers involved a virtually identical figure, we address them together first. We then discuss in turn the alleged falsifications in the Glia and PNAS papers. Since some of the same primary data were used in the figures in the last two papers, we discuss those papers more briefly and incorporate by reference relevant material developed in the section on the PRSL and ANYAS papers.

1. Figure 1 of the PRSL and ANYAS papers

Figure 1 of the PRSL and ANYAS papers contains the same data, described in virtually the same way in the legends, except that the lanes are numbered a through c in PRSL and 1 through 3 in

ANYAS. PRSL paper at 43; ANYAS paper at 257 (note that this paper references the figure as adapted from PRSL, see ANYAS paper at 270, n. 5). Both figures describe the three lanes of data as deriving from a single experiment. The first lane in each figure is described as showing "optic nerve glycoproteins . . . separated by SDS polyacrylamide gel electrophoresis and silver stained." The second lane in each figure is described as resulting from electrophoretically transferring glycoproteins from the first lane to nitrocellulose and reacting them with 7493 antisera. This lane shows a prominent immunoreactive band represented to have a molecular weight of 260 kDa. The third lane is described as similarly transferred glycoproteins from the first lane reacted with pre-immune sera. This lane shows no immunoreactivity.

The figure is allegedly mislabeled in three respects. First, it is uncontested that the two immunoblot lanes do not derive from the silver-stained gel shown in the first lane. Instead, the lanes are drawn from a completely unrelated experiment. The two experiments were performed by two different experimentalists for different purposes months apart. Second, ORI contended that nothing in the primary data from either experiment supports the representation in the legend that any of the lanes derives from optic nerve glycoproteins. ORI Findings #4A, at 40. Third, ORI maintained that the primary data do not support the representation in the figure that the immunoreactive band has a molecular weight of 260 kDa. Id.

Dr. Angelides agreed that the figure is represented incorrectly, in that it does not contain data from a single experiment. Ang. Br. at 184. Further, he did not dispute the identification of the original experimental data in the record before us. Id. However, Dr. Angelides disputed that he was the person responsible for the creation of the figure and therefore for any misstatements in the legend. He asserted that he did not intentionally misrepresent the data. Id. at 185. Further, he argued that the primary data are not sufficiently well-labeled to permit an identification of the tissue source or molecular weight different from that made at the time the figure was prepared. Id. at 194. We therefore consider whether it was established by the preponderance of the evidence that Dr. Angelides both was responsible for including these false identifications in the published papers and intentionally made representations about the data which he knew were false.

a. Primary data for the lanes in Figure 1 of the PRSL/ANYAS papers

The first lane of the figure was located in data generated by Dr. Jeffrey Wood. Dr. Wood worked in Dr. Angelides's laboratory from October 1987 until early 1989 and then transferred to another laboratory at Baylor. Wood WD at 2. It is undisputed that the specific piece of data from which the first lane of the figure was drawn was the fourth lane from the left of a silver-stained gel, a photographic copy of which appears as Record Exhibit 1, at Enclosure II.C.4.12. The data were photographed in a strip of three negatives labeled in Dr. Wood's handwriting. Dr. Wood testified that his practice was to photograph his gels and blots with three exposures of different brightness (to ensure a good print) and then to attach a piece of tape with identifying

label on the resulting negatives. Wood WD at 15-16; Tr. at 861-62 (Wood).[62] The tape label did not specify the date or antigens but read "4-15% gel, Ag Stain, Amersham Markers."

From this information, Dr. Wood was able to identify in his notebook the experiment of November 30, 1988 from which this gel was derived, relying on the number of lanes, the characteristics of staining in the lanes, and the fact that he remembered using Amersham molecular weight markers in only this experiment. Tr. at 865-67 (Wood); Hearing Ex. 8, at 86.[63] Dr. Wood testified that he was "confident enough to make the statement" that the data derived from the November 30, 1988 experiment based on "the standing [presumably what was meant was "staining"] characteristics of the gel" and additional experimental details such as those mentioned.[64] Tr. at 866-67. The tissue sources run are listed in the notebook, and Dr. Wood testified that the samples were run in the order from left to right on the gel corresponding to the notations from top to bottom. Tr. at 853 (Wood). His practice was to load the samples in that order unless otherwise noted. Wood WD at 25. Based on the notebook, Dr. Wood concluded that the silver-stained gel lane used in Figure 1 of PRSL/ANYAS was an extract of rat cerebellar tissue, and not the reported optic nerve glycoproteins. Id. at 26. Furthermore, Dr. Wood was certain that he never prepared optic nerve glycoproteins. Wood WD at 16. The Panel's review of Dr. Wood's notebook corroborated his testimony that he performed only one Western blot analysis with optic nerve, using mAb3, not 7493, and that experiment involved optic nerve

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[62]Dr. Angelides argued that much of Dr. Wood's data from this period was not in the record, given that Dr. Wood testified to having run ten to twelve gels and having generally photographed his results in sets of three negatives. Ang. Br. at 191-92; Tr. at 843-45 (Wood). Some of Dr. Wood's data were in the original records. Hearing Exs. 8, 9. However, the Panel did not find it necessary to consider whether records of the results of some of Dr. Wood's experiments were not available. The significant, and uncontested, facts are that the silver-stained gel came from Dr. Wood's data, not Dr. Elmer's, was not from the same experiment as the blot lanes used in the figure, and could not have been run with the tissue source claimed (because Dr. Wood never used optic nerve glycoproteins).

[63]Dr. Wood testified that Western blots were also done as part of this experiment but that he did not remember what the results were. Wood WD at 17; Tr. at 853. Dr. Wood's notebook contains a notation, which he identified as his, in relation to this experiment, that the "blots were given to Kim for paper." Hearing Ex. 8, at 86. Dr. Wood identified a negative that he believed might represent the results of the November 30, 1988 experiment and noted that it did not show a single prominent band at 260 kDa with the 7493 antibody. Wood WD at 17; ORI Exs. 62 and 63. Dr. Wood testified that he did not construct any figure using that Western blot data and was unaware of any use of it in any published paper. Wood WD at 19.

[64]There is also other information in the notebook that further supports Dr. Wood's identification of the relevant experiment. For example, the notebook contained a standard curve performed on November 29th just before loading samples on gel that is consistent with Dr. Wood's interpretation. Wood WD at 18; Patrick WD at 34.

extracts, not optic nerve glycoproteins. Id. at 13. (He also testified that the only experiment he ran with optic nerve and 7493 was a dot blot, also found in his notebook, which was again extract not glycoproteins. Id. at 12.)

The second lane of Figure 1 of the PRSL/ANYAS papers was located in data generated by Dr. Lawrence Elmer. Dr. Elmer began as a student in Dr. Angelides's laboratory in 1983 at the University of Florida and accompanied him to Baylor in 1986. He left Baylor at the end of June 1988 to start a medical internship in South Dakota, returning to finish his doctoral thesis over several weekends and finally for two weeks in October 1988. Elmer WD at 3. Dr. Angelides did not dispute that the source of the second lane was primary data of Dr. Elmer shown at Record Exhibit 1, at Encs. II.C.4.21 and II.C.4.28 (and the original of which appears in Hearing Exhibit 27). Ang. Br. at 184. Dr. Elmer testified that this experiment was an Olmsted procedure in which he attempted to determine whether the 170 kDa band that he found on Western blots of sodium channel probed with 7493 represented a protein antigenically related to the 260 kDa alpha subunit of the sodium channel in rat brain. Elmer WD at 17. The two left lanes show 7493 antibody binding to partially purified sodium channel with a strong band at 170 kDa, which is noted as the region from which he eluted an anti-170 specific sample of 7493 antibody. Elmer WD at 18-19. The two right lanes represent testing of two dilutions of this sample against "crude glycoproteins." Id.; Record Ex. 1, at Encs. II.C.4.21 and II.C.4.28.[65] Dr. Elmer testified that the tissue source was synaptosomal glycoproteins from rat brain, not rat optic nerve glycoproteins. Elmer WD at 19. He denied that he ever led Dr. Angelides to believe that the antigen used was optic nerve. Tr. at 2026. He further testified that a review of his data made clear that he never conducted any immunoblot with 7493 antibody against rat optic nerve glycoproteins to determine the size of a reaction protein. Elmer WD at 27. The Panel's review of Dr. Elmer's data confirmed that no such experiment was recorded.

b. Responsibility for the creation and publication of Figure 1 of the PRSL/ANYAS papers

The Panel concluded for several reasons, based on the evidence in the record as a whole, that Dr. Angelides was the person responsible for the publication of Figure 1 in PRSL and ANYAS. First, Dr. Angelides was the only author from his laboratory on the ANYAS paper and was the direct source of the figure provided to Drs. Waxman and Black. Second, the two experimentalists involved testified that they were never made aware of how their data were presented in this figure and therefore had no opportunity to correct the misstatements. Third, although Dr. Angelides suggested that the figure was prepared by Dr. Elmer for an earlier

[65]Dr. Elmer stated, and a notation on the data confirmed, that samples eluted from the anti-260 kDa region did not result in immunoreactive antibody. Elmer WD at 18; Record Ex. 1, at Enc. II.C.4.28. The left lanes show no visible bands at the 260 kDa position, which Dr. Elmer attributed to the timing of this experiment in 1987 (before he had optimized a protease inhibitor cocktail that reduced the presence of the 170 kDa species). Elmer WD at 18-19. He also testified that this was the only Olmsted experiment that he remembered performing. Id. at 19.

manuscript, he produced no evidence to support this assertion in the face of the contrary testimony of Dr. Elmer.

The PRSL paper was submitted on February 27, 1989 and published later in 1989. The ANYAS paper was not published until 1991. Dr. Elmer had left Dr. Angelides's laboratory in 1988 and Dr. Wood left by early 1989. Thus, by the time the PRSL paper was being submitted Dr. Elmer had already been gone for months (since it is undisputed that his last working visits occurred before his thesis was defended in October 1988). Dr. Angelides did not acknowledge Dr. Wood as a source of data in either paper. Drs. Waxman and Black testified that Dr. Angelides provided the figure, legend and text for each paper directly, and that they had no contact with Drs. Elmer or Wood at all in the drafting process. Waxman WD at 13; Black WD at 9. They relied on Dr. Angelides, as head of his laboratory, to be in contact with Dr. Elmer about his data. Black WD at 9. These figures were the sole contribution of Dr. Angelides's laboratory to these papers. Id.

There is no evidence that Dr. Angelides ever showed either of the experimentalists involved how their data were being presented. Dr. Elmer testified that he was not involved in "drafting, editing, or reviewing" any manuscripts with Dr. Angelides after the fall of 1988. Elmer WD at 11. While he said he became aware obliquely that a manuscript was submitted to PRSL, he testified that he did not receive a pre-publication copy or any draft. Id. Dr. Elmer stated that he became aware of the PRSL paper in May 1989 (well after its submission) because he received a letter from Dr. Angelides attaching another joint paper with Dr. Waxman on which Dr. Angelides planned to include Dr. Elmer as an author (which became the Glia paper), but mentioning that a new Figure 1 would be provided because this one was the same as the Figure 1 already published in the PRSL paper. ORI Ex. 90A. This communication does not evidence any opportunity for Dr. Elmer to review or verify the presentation of his data in the PRSL paper before its publication. Furthermore, Dr. Elmer testified that he was never made aware of the ANYAS paper including his data in it until the Baylor investigation. Elmer WD at 11. This was consistent with the omission of his name as author. Dr. Elmer testified that he did not at any time, either alone or together with Dr. Angelides, prepare either the display of the data or the legend as presented in Figure 1 of the PRSL or ANYAS papers. Tr. at 2024. He denied that he ever even saw Dr. Wood's silver-stained gel before it was shown to him during the Baylor investigation. Tr. at 2025-26.

Dr. Wood left the laboratory around the time that the first of the two papers was submitted. He was not listed as an author on either paper and was never informed that his data were included in either. Wood WD at 6. In fact, Dr. Wood testified that he never knew (until the Baylor investigation) that any of his data had been included in any published paper. Id. He further stated that Dr. Angelides never provided him with manuscripts or galley proofs of any papers containing his data to him for review. Id. Dr. Wood wrote to Dr. Angelides in March 1989 specifically requesting that his name not be included on any paper. ORI Ex. 57. He testified that he did so because he felt at the time that he did "not trust Dr. Angelides to accurately represent" his data. Wood WD at 10. Thereafter, neither Dr. Angelides nor anyone else from his laboratory contacted Dr. Wood or discussed with him the use of his data for publication. Wood WD at 11.

The conclusion that Dr. Angelides was primarily responsible for the content of Figure 1 is corroborated by Medical Illustrations records. At a point when Dr. Elmer had already left the laboratory and completed his thesis defense, Dr. Angelides instructed that prints be made from Dr. Elmer's data from which the second lane of the figure derived. See ORI Ex. 41, at 1 and 1A (Baylor Medical Illustrations file 135961-C; order dated December 27, 1988 placed by Dr. Angelides). Further, a negative showing Dr. Wood's silver-stained gel data and his identifying notations on the negative strip was found in another Medical Illustrations file ordered in Dr. Angelides's name after Dr. Wood left the laboratory. See ORI Ex. 45, at 10, 26 (Baylor Medical Illustrations file 138161-C; order dated January 26, 1990). Order forms in Dr. Angelides's name in the latter file (with Dr. Wood's data) contained a cross-reference as well to the former file (with Dr. Elmer's data). Id. at 3, 6, 9. While the Medical Illustrations file is not definitive proof that Dr. Angelides constructed the figures in question, it is clear that Dr. Angelides had access to and made use of these primary data of two experimentalists after they had left the laboratory and during a time period consistent with his using these data for the PRSL and ANYAS publications.

Dr. Angelides pointed to the fact that photographs of both sets of primary data were located in Dr. Elmer's records, apparently printed independently of the Medical Illustrations facility, as evidence that Dr. Elmer created the figure. Ang. Br. at 193. A print of these data was found in a folder also containing data of Dr. Elmer during the Baylor investigation, but Dr. Elmer consistently denied that he placed it there or had seen it before and testified that his records and data were left with Dr. Angelides when he left the laboratory in June 1988. Tr. at 2025-26. Dr. Wood's experiment was not conducted until November 30, 1988, and, moreover, he also denied that he gave data to Dr. Elmer. Wood WD at 19. Nowhere in Dr. Elmer's records was any photograph combining lanes from the two independent data sets or any other link to suggest that he was involved in combining them to create the figure at issue. Dr. Elmer's records did include a print of his Olmsted experiment "flipped" left to right (the same orientation shown in the lane drawn from that experiment that is presented in Figure 1). Hearing Ex. 15. However, this photograph could as easily have been the source Dr. Angelides himself used to extract the lane for use in the figure. In other words, even if Dr. Elmer had printed a photograph of his Olmsted experiment "flipped" around, that fact does not make it any more likely that he was aware of Dr. Angelides's use of that data in these papers. In itself, the presence of photographs of Dr. Wood's gel and Dr. Elmer's "flipped" blot data in files turned over to the Baylor Sub-Committee that had been in the possession and control of Dr. Angelides is not sufficient to undercut Dr. Elmer's clear testimony that he did not participate in creation of this figure.

Dr. Angelides's own expert witnesses testified that, if a manuscript is prepared after a student has left a laboratory, the standard procedure would be to contact the experimentalist to review and interpret the primary data and participate in the preparation of the manuscript. Limbird WD at 8; Tr. at 637 (Pfenninger). They agreed that the standards in the scientific community, then as now, required a good faith effort to ensure accurate reporting of others' data. Tr. at 640 (Pfenninger); Limbird WD at 4; see also Waxman WD at 4-5. In fact, Dr. Angelides himself agreed that he had an obligation to consult his students and resolve any questions about molecular weight or

tissue source. See Ang. Br. at 135.[66]. Other scientists agreed that the interpretation of data should be verified with the person who conducted the experiment if the data are not labeled clearly enough to preclude error. See, e.g., Gilbert WD at 34. Dr. Angelides did not include Dr. Wood as an author on either paper and did not include Dr. Elmer as an author on the ANYAS paper, thus taking complete responsibility for the accuracy of the data within the manuscripts. Dr. Wood was still at Baylor, though no longer in Dr. Angelides's laboratory, and Dr. Angelides did not establish that Dr. Elmer would have been difficult to contact. Wood WD at 1-2. By choosing to omit the experimentalist on a paper, Dr. Angelides, at the least, undertook to ensure that their data were accurately presented. Therefore, the Panel concluded that Dr. Angelides had the primary responsibility for the accuracy of the data, since in each case he provided them for publication without seeking the review and input of the actual experimentalists.

c. Intentionality of the misrepresentation of the data in Figure 1 of the PRSL/ANYAS papers

The Panel next considered whether the misstatements in the legend of the figure at issue were likely to have occurred by honest error or interpretation of data, and concluded, on the contrary, that the preponderance of the evidence supported a conclusion that Dr. Angelides intentionally misrepresented the data. The main reasons the Panel reached this conclusion are:

- Dr. Angelides did not claim to have been confused in compiling this figure after the departure of the two experimentalists, but rather denied responsibility for its creation. Ang. Br. at 189. As noted above, the Panel found that Dr. Angelides, not Dr. Elmer, was responsible for the creation and publication of this figure. It was not credible that Dr. Elmer either accidentally or intentionally misrepresented the data in the manner found here.

- The figure was constructed from the original data of two different experimentalists created at widely different times. Dr. Elmer's Olmsted experiment was performed in the summer of 1987 and Dr. Wood's silver-stained gel came from an experiment in November 1988. Elmer WD at 18; Wood WD at 16. This reduces the likelihood of accidental error, since Dr. Angelides alone had access to and control of both data sets.

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[66]While Dr. Angelides argued that he actively consulted with the students at the time these experiments were performed, and the testimony of the experimentalists is that they indeed kept him informed of their results on these important experiments, Dr. Angelides did not provide any credible evidence that he consulted with them about the way their data were presented in this figure (or in the other papers) to ascertain the accuracy of his interpretation. See Ang. Br. at 135-38. Both experimentalists testified that they had discussed the results of these experiments with Dr. Angelides and denied that the information they gave Dr. Angelides about their experiments could have been interpreted in any way consistent with the claims made in these papers. Elmer WD at 19, Wood WD at.

- No notations in the primary data provide any support for the representations made that the immunoreactive species had a molecular weight of 260 kDa or that the tissue source used was optic nerve glycoproteins, so that such misrepresentations were unlikely to occur accidentally, by the choice of the inappropriate gel.

- The misrepresentations were favorable to the documentation of a significant accomplishment by Dr. Angelides's laboratory for which no other legitimate data have been shown to have existed.

Dr. Angelides did not argue in his defense that he had difficulty interpreting the data used in this figure because the experimentalists involved were unavailable to assist in interpreting the aspects that were not clearly labeled. Instead, he attributed responsibility for any errors in the paper to Dr. Elmer on whom Dr. Angelides relied as the experimentalist. Dr. Angelides claimed that the figure and legend were actually prepared by Dr. Elmer before Dr. Elmer left the laboratory, as part of preparing an earlier manuscript draft, and then later simply were removed for use instead in the PRSL and ANYAS papers. Tr. at 1401, 1419 (Angelides). Thus, Dr. Angelides contended that the figure was made while both Dr. Wood and Dr. Elmer were still in the laboratory. See also Angelides Resp. to Baylor Report at 166-167. Dr. Angelides asserted that Dr. Elmer told him that the lanes used in Figure 1 represented optic nerve glycoproteins and showed a protein recognized by 7493 of 260 kDa molecular weight. Tr. at 1418. He attributed any mistake in the figure to Dr. Elmer's "inadvertent error due to the fact of Dr. Elmer's labeling and record-keeping," while denying that there was "anything intentional on Dr. Elmer's part, at all." Tr. at 1433-34 (Angelides).

In support of this scenario, Dr. Angelides pointed to a print-out of one version of an earlier manuscript (for what later became the Brain Research paper) in which a figure legend described a planned 18-lane figure including one lane (the twelfth) of "optic nerve" probed by polyclonal antibody visualized by ^{125}I-Protein A in autoradiography. Record Ex. 43, at 234, 269 (referred to as the Voltage.kja draft, dated Oct. 7, 1988). A similar figure legend was included in an even earlier draft in Dr. Angelides's handwriting. See Ang. Ex. 10 (Bates-stamped page 016592). Dr. Angelides did not produce any version of the manuscript that contained data corresponding to this figure legend. He asserted that data existed at the time from which such a composite figure could have been constructed. Tr. at 1735-36. However, he never produced the corresponding data. Therefore, the Panel concluded that, while the researchers may at one time have planned to test 7493 by immunoblotting against all of the tissues identified in the draft figure legends, there is no evidence that any Western blot data using optic nerve glycoproteins ever existed.

Certainly, the intended 18-lane figure described in the legend would not have resembled the figure presented in the PRSL/ANYAS papers. First, the legend to the draft paper described visualization using ^{125}I-Protein A, while, in Figure 1 of the PRSL/ANYAS papers, the antibodies were conjugated with alkaline phosphatase. Confronted with this inconsistency, Dr. Angelides testified that the description in the draft manuscript was an error, and that alkaline phosphatase

was used. Tr. at 1732 (Angelides); compare Record Ex. 43, at 269 with PRSL paper at 42. The draft manuscript figure legend contained no mention of a silver-stained gel lane such as appeared as the first lane in the PRSL or ANYAS figure, and does not describe a figure in any way resembling that used in the PRSL and ANYAS papers. Thus, even if Dr. Angelides were correct in claiming that one of the lanes of a putative 18-lane array was removed for use in the PRSL and ANYAS figure, that would not explain how it came to be associated with an unrelated silver-stained gel and then misidentified as we have found it in the PRSL and ANYAS figure.

The Panel found it difficult to arrive at any plausible scenario involving honest error by Dr. Elmer as the cause of the false identification of these data. It is very unlikely that Dr. Elmer could have mistakenly presented an inappropriate gel as optic nerve if, as he testified, he had never even conducted Western blots with optic nerve. Dr. Angelides contradicted this testimony and claimed that many records exist in Dr. Elmer's files showing the probing of optic nerve with antibodies. Tr. at 1433. However, neither Dr. Angelides's briefs nor the Panel's independent review of Dr. Elmer's records revealed a single example of a Western blot of 7493 probing optic nerve extract or glycoproteins. It is also unlikely that Dr. Elmer could accidentally mistake for his own the silver-stained gel data generated by Dr. Wood, especially since both researchers deny that they were conducting any joint experiments or sharing data. Elmer WD at 62-63; Wood WD at 19. Furthermore, by the time Dr. Wood generated the gel at issue, Dr. Elmer had already left the laboratory. Therefore, the possibility of inadvertent error by Dr. Elmer seems remote, which undercuts the possibility that Dr. Angelides reasonably relied on Dr. Elmer who innocently misled him. Logically, therefore, either Dr. Elmer or Dr. Angelides knowingly falsified the description of these data.

The Panel also found it implausible that Dr. Elmer would have intentionally misrepresented to Dr. Angelides the nature of the data included in Figure 1. Notably, Dr. Elmer did not include any data on optic nerve in his thesis. Hearing Ex. 25. Had he been intentionally misleading Dr. Angelides about having performed Western blots of optic nerves, it seems likely he would have included the same claims in the thesis he was also preparing in October 1988. Hearing Ex. 25. Further, Dr. Elmer knew that Dr. Angelides had access to the primary data of all present and former researchers in the laboratory. Therefore, it is difficult to see why Dr. Elmer would choose to misuse data of another laboratory member in combination with data from his own records to create such a figure, given the risk that either Dr. Angelides or Dr. Wood (who did not leave until after the PRSL paper was submitted) might recognize that the data did not belong to Dr. Elmer at all, much less to the purported experiment. Further, it is unlikely that, had he misrepresented these data to Dr. Angelides, Dr. Elmer would have retained and left in his records with Dr. Angelides the correctly-labeled primary data.

Based on this analysis, the Panel concluded that Dr. Angelides's claim that the data were misidentified by Dr. Elmer was an inappropriate attempt by Dr. Angelides to redirect responsibility for his own failures. Further, the Panel concluded that this effort to shift blame was in itself evidence of consciousness of guilt and therefore increased the likelihood that Dr. Angelides acted intentionally in presenting false information about these data in these papers.

The Panel concluded that this conduct makes it unlikely that the misrepresentations resulted from honest error or interpretation of data.

In addition, the Panel noted that not only are the three lanes not from a single experiment, as claimed, they are drawn from the unrelated work of two different laboratory members widely separated in time. At the time the figure was first submitted in February 1989, Dr. Angelides had access to the data of both experimentalists. Dr. Elmer's experiment had no silver-stained gel associated with it, so that it is not possible that somehow two different silver-stained gels were interchanged. Elmer WD at 69. Dr. Wood testified that he gave data from this particular November 30, 1988 experiment to Dr. Angelides for possible use in a paper (although he was never informed that any of his data were actually used in a paper), and a notation in his notebook corroborated this. Wood WD at 17-19; Tr. at 858-61; Hearing Ex. 8, at 86. The fact that Dr. Angelides alone had access to and information about both data sets further enhances the likelihood that it was he who intentionally misrepresented the data.

We turn next to whether the specific misidentification of molecular weight and antigen was likely to have been intentional. In presenting the data in the figure, Dr. Angelides described this experiment as testing 7493 antibody against optic nerve with the result that a prominent band was seen with a molecular weight of 260 kDa. However, neither piece of primary data contains any notations that would support the claim that the band seen was at 260 kDa or that the tissue source involved was optic nerve. As to the molecular weight, the band on the lane that Dr. Angelides used from the Olmsted experiment was shown as on the same level as a region of the lane from which anti-170 7493 antibody was eluted. Hearing Ex. 27. Dr. Elmer testified that the lane used was from a Western blot testing the anti-170 antibody and the band obtained was at 170 kDa, with no reactivity obtained at 260 kDa.[67] Elmer WD at 18. Dr. Elmer testified that this Olmsted experiment was a critical step in his research which he discussed several times with Dr. Angelides and for which he had shown Dr. Angelides the resulting data, so that he believed Dr. Angelides was well aware of the nature and results of the experiment. Elmer WD at 19, 65; Tr. at 2029 (Elmer). He denied that he ever led Dr. Angelides to believe that the immunoreactive species in this lane was at 260 kDa. Tr. at 2029 (Elmer); but cf. Angelides Resp. to Baylor Report at 68. Dr. Elmer said that he based his judgment of the molecular weight on molecular weight markers run with the gels at the time, although he did not include the markers in the array he prepared to show the results of the Olmsted experiment, so that his labeling of the 170 kDa

[67]He stated that he also attempted to elute anti-260 antibody and tested it, but that he did not note the region from which it was eluted or show the lanes from the Western blot test, because he was unable to get any immunoreactivity. Tr. at 2027, 2037-38 (Elmer). A notation to that effect is on the original array of lanes from the Olmsted experiment. Hearing Ex. 27.

location was accurate at the time the experiment was run. Tr. at 2028-29 (Elmer).[68] Dr. Angelides's expert witness, Dr. Pfenninger, testified that he would have no basis to disagree with the experimentalist if the experimentalist verified (as Dr. Elmer did here) the molecular weight as 170 kDa based on molecular weight markers run at the time on the same experiment. Tr. at 589.

As far as the tissue source, neither the Olmsted experiment array nor the silver-stained gel photograph specifies the tissue source, so Dr. Angelides had no discernable basis for claiming that optic nerve glycoproteins were used. The Olmsted experiment array states only that "crude glycoproteins" were used. Hearing Ex. 27. Dr. Elmer testified that the experiment was done with crude rat brain synaptosomal glycoproteins. Elmer WD at 18-19. He testified that the purpose of the experiment was to determine whether the 180 kDa band was a breakdown product related to the sodium channel alpha subunit (of 260 kDa) in rat brain, so the use of rat brain synaptosomal proteins is logically connected with the point of the experiment. Elmer WD at 19. He further testified that it was his general practice to use rat brain synaptosomal glycoproteins to screen antibodies, and that he would have made a note if he used another tissue. Elmer WD at 28; see, e.g., ORI Ex. 74 and Record Ex. 1, at Enc. II.C.4.42. In addition, he testified that he never conducted immunoblots with 7493 against rat optic nerve. Elmer WD at 27.[69] The Panel concluded that Dr. Angelides did not obtain information from the primary data or from the experimentalist to support a claim that optic nerve glycoproteins were used.

As noted above, while the photograph of the silver-stained gel does not itself include any identification of the tissue source in the different lanes, Dr. Wood was able to locate the experimental protocol which listed the tissue sources and testified that the lanes in the gel followed the same order as in the protocol (since that was his regular practice unless otherwise noted). Tr. at 834, 853, 865 (Wood). Besides the factors which he relied on to identify the experiment from which the silver-stained gel derived (including the number and banding patterns of the lanes and the use of Amersham markers), Dr. Wood was certain for additional reasons that the lane used from it in Figure 1 of PRSL/ANYAS could not have contained optic nerve

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[68]Dr. Elmer also pointed out that the 170 kDa species was the predominant band with which 7493 reacted at this time in his research, although later he was able to achieve better results at 260 kDa (the expected size of the intact alpha sub-unit of the sodium channel) in 1988 after discovering a protease-inhibiting procedure to use in preparation for immunoblotting. Consequently, it was highly unlikely that Dr. Angelides could have assumed that this experiment from mid-1987 showed 7493 reacting with a species of molecular weight of 260 kDa. In fact, if anything, were Dr. Elmer to have made such a representation to Dr. Angelides at the time, given the other data which were showing the predominance of the lower weight species, Dr. Angelides could have been expected to question how the change was achieved.

[69]Since rat optic nerves make up such a very small fraction of the mass of the brain, preparing optic nerve requires considerable amounts of dissection. Consequently, it is likely that Drs. Wood and Elmer would remember preparing and using optic nerve glycoproteins if they had done so.

glycoproteins as claimed in the legend. First, Dr. Wood testified that he never performed a Western blot with rat optic nerve and 7493 antibody.[70] Wood WD at 12. While he did test monoclonal antibodies in Western blots against optic nerve extract, he testified that he never even prepared optic nerve glycoproteins, as claimed in the legend to Figure 1 of PRSL/ANYAS. Id. at 13. Dr. Wood testified that when he ran immunoblots of 7493 antibody against other tissues, he always found either no bands at all or multiple bands, so that he had no results that resembled those claimed in the figure legend. Wood WD at 14-15; see ORI Ex. 61. Upon examination, the Panel found that the testimony of Dr. Wood concerning his experiments was consistent with his notebook. Hearing Ex. 8.

The Panel thus concluded that Dr. Angelides had no basis for his representation that any of these data were derived using optic nerve glycoproteins.

The significance of the misrepresentations in the questioned data to the research reported in the papers is evident in a close reading of the papers themselves. The abstract of the PRSL paper stated prominently that 7493 antisera "recognizes a 260 kDa protein in immunoblots of crude glycoprotein fraction from adult rat optic nerve." PRSL paper at 39. The paper noted that other probes had proven either unsuitable for use with fixed tissues for ultrastructural studies or limited to use with electric eel organs. Id. Consequently, immuno-electron microscopy of mammalian sodium channel distribution had not been possible before, until this study which relied on 7493 "as an immuno-ultrastructural probe to examine the localization of sodium channels within rat optic nerve" providing "the first demonstration of sodium-channel immunostaining at an ultrastructural level in the mammalian central nervous system." Id. at 41. In the discussion section, the paper plainly states that the "utilization of antibody 7493 as an immuno-ultrastructural probe for the localization of sodium channels within the central nervous system is dependent upon characterization of the specificity of the antiserum." Id. at 45. This characterization is reported to be based on several lines of evidence, including the ability of 7493 to recognize sodium channel in rat brain glycoproteins and purified channel and to immunoprecipitate sodium channel. Further, based on the results in Figure 1, the study finds that "the reactivity of the antibody extends to glycoproteins from rat optic nerve; on immunoblot analysis, 7493 antisera recognize a diffuse band of M_r 260000, corresponding to the mobility and migration of the alpha subunit of the sodium-channel protein." Id. at 46. The ANYAS paper also reported research that relied on the "new immunocytochemical methods" (citing, inter alia, the PRSL paper) to conduct further research on the distribution of sodium channels in astrocytes in rat optic nerve, including the use of 7493 as a "specific immunocytochemical marker that permits localization of sodium channels at both the light and electron microscopic level." ANYAS paper at 255-56. This ability is reported based on the figure that is reported to show that 7493 "selectively immunostains a protein with an M_r of 260 kD, corresponding in migration and mobility to the á subunit of the rat brain sodium channel, after separation of crude glycoproteins from adult rat optic nerve . . . ." Id. at 256.

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[70]He did do a dot blot analysis that included optic nerve, but that would yield only initial information about reactivity and would give no indication of molecular weight. Wood WD at 12.

Dr. Angelides contested the materiality of the misrepresentations to the papers at issue, contending that ORI did not advance "an opinion on the objectives or significance of the data" in each of the papers at issue. Ang. Br. at 126-27. However, in each case, the significance of the data presented in the contested figures was testified to by the co-authors and was evident to the Panel on its reading of the papers themselves. These misrepresentations are material even if the 7493 antibody could indeed detect the á subunit of the sodium channel in the rat optic nerve. At question is not the utility of the antibody but the validity of the claims made about it in these papers at the time.

As to the PRSL paper, Dr. Angelides argued that its central finding was the "substantiation of previously-reported results . . . using 7493 as a tool" confirming sodium channel localization results. Ang. Br. at 126. He contended that the success of the electron microscopy itself sufficed to independently demonstrate the utility of 7493 and therefore to reduce the importance of the immunoblotting results.

However, Dr. Black testified that it was extremely important to the co-authors that the specificity have been demonstrated in the same tissues for which the antibody was being used in immunostaining studies. Black WD at 10. Dr. Waxman testified that, if the data in Figure 1 of the ANYAS and PRSL papers were false, the interpretation of the electron microscopy results would be substantially affected because he would not then be able to conclude definitively that what was stained was sodium channel protein. Waxman WD at 13; see also Patrick WD at 21-22 (data in Figure 1 were essential to establish utility of 7493 as a probe to detect only sodium channel protein in optic nerve glycoproteins).

Dr. Angelides also attacked the opinion of Dr. Gilbert that the misstatements about the data in the figure "helped validate the immunolocalization of the sodium channel in sections of optic nerve described in the rest of the paper, so it was important to show that the 7493 antibody recognized a single protein in tissue extracts of optic nerve" as unfounded because Dr. Gilbert did not demonstrate specific expertise in the sodium channel field in 1989. Gilbert WD at 38; Ang. Br. at 183. Instead, Dr. Angelides argued that the PRSL co-authors wanted to report their successful use at the ultrastructural level of an antibody labeling sodium channels at nodes of Ranvier, which had previously been found in eel tissue axons and with other methods. Ang. Br. at 183-84. Even accepting Dr. Angelides's characterization of the goals of the ultra-structural research, his arguments do not effectively counter the co-authors' testimony that their assessment of the electron microscopy depended on their acceptance of the representations in the data provided by Dr. Angelides of the specificity of the antibody in the target tissue as accurate. Furthermore, the Panel's determination as to the materiality of the demonstration of the reported specificity of the antibody for the sodium channel in optic nerve does not depend on the level of expertise of Dr. Gilbert but rather is evident both in the texts of the papers themselves and from the testimony of the co-authors.

Dr. Angelides thus had substantial incentive to provide these data for the paper in order to establish that the polyclonal antibody developed in his laboratory had been shown both to be

reliably specific for the 260 kDa protein of the sodium channel and capable of recognizing that protein specifically in optic nerve glycoproteins. Dr. Angelides has not identified any publication prior to the PRSL paper attesting to the specificity of the 7493 antibody. Notably, Dr. Angelides has not been able to identify any data from his laboratory that would have supported the claim made in the figure that 7493 will recognize a single band at 260 kDa in optic nerve glycoproteins. Were Dr. Angelides to have demonstrated that alternative data were available in the laboratory records that would support the claim, the contamination of the literature would have been significantly less substantive and the evidence that he had a motive to intentionally misrepresent the data here would have been less compelling. However, given the strong incentive to provide data of this kind for this paper and the evident absence of any authentic data supporting the claim, Dr. Angelides had a strong motive to make the misrepresentations found here. Furthermore, a scenario whereby this combination of unrelated lanes of data could have been constructed and falsely labelled through unintentional error alone is difficult to conceive. The Panel therefore concluded that the weight of the evidence indicates that the false labeling of this figure was intentional.

Numerous scientists testified that the intentional misrepresentation of data or experimental results in a scientific publication seriously deviated from the standards of the scientific community, both now and in 1989. See, e.g., Black WD at 4; Waxman WD at 4; Gilbert WD at 6; Tr. at 593, 640 (Pfenninger). The Panel concluded that such intentional misrepresentation would constitute scientific misconduct both before and after the adoption of the DHHS regulatory definition. See 45 C.F.R. § 50.102.

Based on the record as a whole, and after considering the arguments of both parties, the Panel concluded that it was established by a preponderance of the evidence that Dr. Angelides intentionally misrepresented the data in Figure 1 of the PRSL and ANYAS papers in the three respects discussed above. The Panel further concluded that these intentional misrepresentations constituted scientific misconduct.

d. Additional arguments offered by Dr. Angelides on this issue

Dr. Angelides argued that ORI's case wholly depended on its claims that the Medical Illustrations files demonstrated that Dr. Angelides alone created the figure, and he denied that the files sufficed to prove this claim. Ang Br. 184-85. He argued that the files did not contain a final publication-ready composite or evidence that Dr. Angelides requested such a final composite and that copies of some of the data used in Figure 1 were in other Medical Illustration files, including one created by Dr. Berget from the Baylor Sub-Committee. Id., cf. ORI Ex. 46. He also asserted that his name on Medical Illustrations files did not establish that he personally made the requests, rather than having been listed as a laboratory identifier. Ang. Br. at 185, n.138.

Dr. Angelides's premise is incorrect, in that ORI's charges against him on this issue depended on the greater array of documentary and testimonial evidence discussed above and not solely on the Medical Illustration files. We have independently reviewed all of this evidence and reached the

conclusion that Dr. Angelides intentionally falsified this figure. The main relevance of the Medical Illustrations evidence to our analysis of this issue lies not in tracing the precise development from the original primary data to the final figure, but in the clear evidence that Dr. Angelides, and no other researcher, was requesting photographic production using the relevant data at the relevant time. It is therefore not dispositive that the files do not show the final creation of the composite or the "flipped" lane that was ultimately included from Dr. Elmer's experiment. The important point is that, in December 1988, when the Medical Illustrations file requests at issue were generated, Dr. Elmer was not in the laboratory, so that Dr. Angelides's name cannot have been placed on the file as an identifier for Dr. Elmer. Dr. Angelides did not suggest any other researcher who could have been seeking prints of these data.

Dr. Angelides argued that Medical Illustrations file 135961 was opened on January 27, 1988 by Dr. Elmer and contained a request from Dr. Elmer to match the silver-stained gel lane with the Western blot lane from Dr. Elmer's experiment. Ang. Br. at 186. This is simply incorrect -- the file does not show Dr. Elmer, but rather Dr. Angelides as the original requester and the client who was billed in January 1988. See ORI Ex. 41, at 1, 11. In addition, the page cited as instructions to match the gel and blot lanes has nothing to link it with Dr. Elmer. ORI Ex. 41, at 13.[71]

It is also not significant, as Dr. Angelides claimed, that this Medical Illustrations file does not contain the silver-stained gel lane nor a reference to take it from another file. Ang. Br. at 187. In fact, the silver-stained lane appeared in another Medical Illustrations file 138161-C with a request from Dr. Angelides dated January 26, 1990 and with a cross-reference to Medical Illustrations file 135161-C which contained Dr. Elmer's data. Contrary to Dr. Angelides's contentions, ORI did not charge that this file constituted the request to construct the figure used in the PRSL paper submitted in February 1989. Rather, this file evidences that, at a time when the ANYAS paper would have been in preparation and when neither Dr. Elmer or Dr. Wood could have been using Dr. Angelides's name to make requests, Dr. Angelides was seeking prints in a way that tied together the disparate primary data and showed that he was handling them directly, apart from simply reusing a figure prepared in completed form by Dr. Elmer, as he had claimed.

Dr. Angelides further argued that neither set of primary data was labeled clearly as to antigen or molecular weight. Ang. Br. at 188. Thus, Dr. Angelides denied that the figure materially misrepresented the primary data, in that he denied that the data were identified clearly enough to determine that the antigen was not optic nerve or that the molecular weight was not 260 kDa. On that basis, he contended that deference should be given to the interpretation of the data made by the researchers themselves in 1988 rather than retrospectively reevaluated now. Ang. Br. at 194. Dr. Angelides's position ignored the testimony of both researchers involved, who the Panel determined have credibly denied that they ever proffered the interpretations of their data which

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[71]No testimony was offered to the Panel about whose handwriting appears on the page or the meaning of the instructions there, which are not clear.

Dr. Angelides put forth in the PRSL and ANYAS figures. Dr. Angelides himself acknowledged that as principal investigator and corresponding author, he had "an obligation to ensure that the correct data is used." Ang. Br. at 193. Yet he asserted that he had "no reason to re-consult the data." Id.

As to the molecular weight, Dr. Angelides argued that the lane used from Dr. Elmer's experiment had no molecular weight markers shown and could therefore not be reliably interpreted as to molecular weight even by an expert. Ang. Br. at 194; Tr. at 1418 (Angelides); cf. Pfenninger WD at 21; Tr. at 583, 587 (Pfenninger). However, even Dr. Angelides's expert witness, Dr. Pfenninger, acknowledged that he would have no basis to disagree with Dr. Elmer's assignment of the molecular weight as shown at 180 kDa, given Dr. Elmer's testimony that he ran markers with the blot at the time. Tr. at 588-89 (Pfenninger). Further, Dr. Angelides argued that photographs printed in reverse and showing only part of the array would make it impossible to discern any reference to molecular weight. Ang. Br. at 188-89. He asserted that ORI had failed to establish that "the photographic print capturing the image of these data contained the information that would have altered Dr. Angelides opinion that it may have been inaccurately included in the draft manuscript that included optic nerve." Ang. Br. at 189. This line of argument ignores Dr. Angelides's continuous access to the underlying primary data, which contained the full array, and to the researcher who generated it. If he had any uncertainty about the molecular weight designation, he could and should have reviewed the primary data and not relied on a photograph (flipped or otherwise). If any uncertainty remained, he could and should have consulted the experimentalist.

As to the antigen tissue source, Dr. Angelides argued that ORI denied that the source was optic nerve but offered no alternative, and that ORI relied on "only selected pages of Dr. Wood's notebook." Ang. Br. at 190, referencing ORI Ex. 58. These arguments lack any merit. As discussed above, the experimentalist who generated the data, Dr. Wood, not ORI, identified the "alternative" tissue source as rat cerebellar tissue extract. Wood WD at 16. The selected pages of Wood's notebook were included in ORI's pre-hearing exhibit submission, but the entire original notebook was received as a hearing exhibit and was available to the Panel. Hearing Ex. 8. As noted above, the Panel searched Dr. Wood's notebook for any reference to optic nerve glycoproteins and found none.

Dr. Angelides further argued that ORI's only basis for concluding that optic nerve was not used in the silver-stained lane in the figure was because Dr. Patrick connected a negative from a Medical Illustrations file with Dr. Wood's November 30, 1988 experiment and then ORI solicited Dr. Wood's testimony in support of this "tenuous hypothesis." Ang. Br. at 191. As indicated above, the Panel independently considered the evidence concerning this lane, and found Dr. Wood's testimony about his experimental data to be credible and consistent with the evidence as a whole. Dr. Angelides did not suggest any reason that Dr. Wood would have misled him as to the experimental source of the gel at the time or would have been motivated to lie about it before this Panel. Thus, our identification of the lanes in the experiment depends not on

the location of a negative in any Medical Illustration file nor on any extrapolation by Dr. Patrick, but on the testimony and notebook of the actual experimentalist.

Dr. Angelides also challenged Dr. Elmer's credibility in asserting before this Panel that he (Dr. Elmer) did not perform any immunoblot with 7493 antibody against rat optic nerve glycoproteins to determine the size of a reaction protein. Ang. Br. at 189; cf. Elmer WD at 27. Dr. Angelides asserted that, in testimony before the Baylor Sub-Committee, Dr. Elmer was less certain, testifying only that he did not remember doing optic nerve experiments but that it was possible such a tissue panel might exist, since he had not reviewed his data. See Ang. Br. at 189-90, nn. 143, 144. The Panel does not consider Dr. Elmer's present testimony to be inconsistent with his statements before the Baylor Sub-Committee. First, before Baylor, Dr. Elmer stated strongly that he did not remember ever using optic nerve, although he stated it might have been done by someone else or for a tissue panel. Ang. Ex. 98 at 134, 137-139. Second, Dr. Elmer's assertion to us was narrow -- not that he never did any experiment with optic nerve but that he never tested optic nerve glycoproteins on a blot with 7493 (that is, he never performed an experiment like that reported in Figure 1). Third, by the time he testified before the Panel, he had had the opportunity to review all of his records and data and, therefore, to speak with more certainty.

Ultimately, none of Dr. Angelides's arguments had merit. In the face of the overwhelming evidence, including the testimony and records of the original experimentalists, that the data were not what Dr. Angelides had claimed, he had to show some basis for the claims which he published. That he failed to do.

e. Conclusion regarding Figure 1 of the PRSL and ANYAS papers

For the reasons explained above, the Panel concluded that the record as a whole established by a preponderance of the evidence that Dr. Angelides was responsible for the presentation of data in Figure 1 of the PRSL and ANYAS papers. Further, the Panel concluded that the record as a whole established by a preponderance of the evidence that Dr. Angelides intentionally falsified those figures by misrepresenting the experiments from which the data were drawn, misrepresenting the molecular weight of the immunoreactive band in the second lane of each figure, and misrepresenting the tissue source of the proteins tested as optic nerve. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive, and that the conduct proven constituted scientific misconduct.

2. Figure 1 of the Glia paper

The Glia paper also employed 7493 antibody in immuno-electron microscopy in the adult rat optic nerve, but concentrated on the patterns of immuno-staining found in astrocyte processes. Glia paper at 354. The abstract reports that antibody 7493 recognizes a 260 kDa protein in "immunoblots of crude glycoproteins from adult rat optic nerve." Id. at 353. This claim is documented by Figure 1 which purports to show a silver-stained gel lane of optic nerve glycoproteins with two lanes of immunoblots of crude glycoproteins transferred from the lane 1

gel. Lane 2 is reported to be an immunoblot with 7493 antibody showing selective immunostaining of "a major protein with apparent Mr 260 kDa ... corresponding to the alpha subunit of the rat brain sodium channel." Id. at 355. Lane 3 is reported to be an immunoblot with preimmune serum showing no immunoreactivity. ORI charged that these claims were intentionally falsified because the glycoproteins from lane 1 were not probed in lane 2, the antigen was not crude glycoproteins and the tissue source was not rat optic nerve. ORI Findings # 4B, at 44.

Dr. Angelides denied intentionally misrepresenting the data in Figure 1 of the Glia paper. He argued that Dr. Elmer's original data are difficult to interpret as to molecular weight. He argued that Dr. Elmer was responsible for the presentation of the data in the figure and participated in preparation of the Glia paper.

a. Primary data for the lanes in Figure 1 of the Glia paper

The first lane in Figure 1 of the Glia paper was again matched to a lane in the photograph of a silver-stained gel which Dr. Wood identified as deriving from the experiment in his notebook dated November 30, 1988. Wood WD at 16-18. However, the lane used was different. Dr. Wood was able to recognize the particular lane used based on visibly distinctive features of the lane. Wood WD at 20.[72] Based on the same protocol listing of the order in which proteins were listed, Dr. Wood identified the protein source in the lane used in Figure 1 of the Glia paper as cortex. Id. Dr. Wood testified that the lane is not optic nerve glycoproteins. Id.

The second lane in Figure 1 of the Glia paper again matched a lane from Dr. Elmer's Olmsted experiment, but here too a different lane was used. In this figure, the far-left lane (rather than the third from the left) was used, also flipped in mirror image. A notation appears in the original primary data directly beside the left-most lane indicating that anti-170 kDa antibody was eluted from the region of the prominent band, yet this band was represented in the Glia paper as at a molecular weight of 260 kDa. Dr. Elmer testified that this left-most lane was, as labeled, a partial purification of the sodium channel from rat brain synaptosomes. Tr. at 994.[73]

b. Responsibility for the creation and publication of Figure 1 of the Glia paper

Much of the discussion about the responsibility for the creation and publication of Figure 1 in the PRSL/ANYAS papers also applies to the Glia paper figure. Dr. Wood testified that he was not consulted at all in relation to the preparation of this manuscript or the figure using his data. Wood WD at 22. He further testified that he was never aware that these data would be used by Dr. Angelides. Id. Dr. Elmer denied that he was informed of the presentation of his data in this manuscript before it was published. Elmer WD at 62.

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[72]Dr. Wood also noted that the first two lanes of the silver-stained gel had similar patterns. This was consistent with his conclusion that the experiment involved was the one recorded on November 30, 1988 in his notebook, because the first two lanes loaded in that experiment were of rat cerebellum and rat cortex extracts, which would produce these similar patterns. Wood WD at 20-21. Moreover, the Panel observed during its review of Dr. Wood's notebook that Dr. Wood did not routinely use these two tissues as the first two lanes, which further supported his identification of these data.

[73]Unlike the third lane in Figure 1 of the PRSL/ANYAS papers, whose source was never identified, the third lane in the Glia paper was identified by Dr. Wood as identical to a lane shown in yet another strip of negatives labeled on a tab in his handwriting as "Mab 3." Wood WD at 21; ORI Exs. 66 and 67. He testified that this blot was done with monoclonal antibody 3, which was recorded in his notebook as having been used in this experiment, and not with pre-immune sera, which he did not use. Wood WD at 21. However, ORI did not charge Dr. Angelides independently with falsification in regard to the third lane of this figure.

However, Dr. Angelides pointed to the May 2, 1989 letter (mentioned above because it contained a reference to the prior PRSL paper) that he sent to Dr. Elmer with a manuscript draft of the Glia paper as evidencing that Dr. Elmer was aware of and actively involved in the preparation of this paper. Ang. Br. at 167; see ORI Ex. 90A. Consequently, Dr. Angelides argued that Dr. Elmer must have approved of the presentation of his data at the time of the publication. Ang. Br. at 167-68.

The letter reads as follows, in relevant part:

> I . . . don't know why I keep putting your name on papers but feel that your contributions were essential to the work. Accordingly here's yet another one that has been submitted by Steve [Waxman] & colleagues. However I told them (I didn't see the final before it was sent) that I didn't think it was correct to use the same Figure (Fig. 1 of the blot) as in the Pro. Roy. Soc. paper and so I'll be sending them a different experiment. This just goes against my principles. In any event the original monographs look good. We have also submitted an abstract to Neuroscience with your name so if that's OK.

ORI Ex. 90A. On the same day, Dr. Angelides wrote a letter to Dr. Black at Yale that read in relevant part: "I think that a different experiment should be used for Figure 1, the immunoblot, since this was used in the Proc. Roy. Soc. Lond. paper. This Figure with a new experiment is now being prepared and I shall send it on by next week." ORI Ex. 90. (The manuscript was initially received April 26, 1989 and not accepted until June 10, 1989, which is consistent with Dr. Angelides providing a revised figure in the interim.)

Dr. Angelides testified that reviewing these letters refreshed his recollection of the circumstances and that Dr. Waxman had submitted the paper to Glia reusing the PRSL figure. Tr. at 1443-44. Dr. Angelides further testified that the letter forwarding the manuscript to Dr. Elmer disproved Dr. Elmer's contention that Dr. Angelides did not regularly provide him with access to draft manuscripts to examine how his data were used. Tr. at 1443-44 (Angelides). Dr. Angelides suggested further that his letter to Dr. Black pointed to the "fast track" in which the Yale co-authors were rushing to publish this material, even before the Brain Research paper (which more fully characterized the 7493 antibody) was submitted, possibly resulting in "inadvertent and unintentional errors in the assembly and submission of this Glia paper." Tr. at 1445-46 (Angelides).

The Panel does not find that this correspondence evidences any involvement of Dr. Elmer in the presentation of data in the figure finally published in Glia, nor any responsibility of the Yale co-authors for the misstatements about the data in that figure. In fact, the clear import of both letters was that Dr. Angelides promised to prepare a new figure to replace the one used in the PRSL paper. We do not read the statement that a "new experiment is now being prepared" to mean that new bench experiments were necessarily being undertaken to document specificity in optic nerve, as Dr. Black understood from this letter. Cf. Tr. at 1940 (Black). However, the letter certainly

implies that, at the least, data from a different experiment were in the process of being newly prepared into a figure suitable to substitute for the one used in the PRSL paper to demonstrate the specificity of 7493 in optic nerve. Yet the figure that Dr. Angelides proceeded to prepare and send came from precisely the same experiments.

The draft sent to Dr. Elmer obviously did not contain the final version of the figure, since Dr. Angelides asserted in the letter that he was going to send a substitute figure. Although he claimed to recall sending to Dr. Elmer "every single manuscript" of every paper with which he was associated, Dr. Angelides did not proffer any later correspondence to Dr. Elmer forwarding the proposed substitute figure for his review. Tr. at 1462. Dr. Elmer testified that he never received any final draft, galley proofs, or even reprints after publication from Dr. Angelides; instead, he had to review the publication at the library. Elmer WD at 61; Tr. at 992-93 (Elmer). He further testified that, when he did see the figure, he thought the data shown there were "beautiful," and he called Dr. Angelides to ask who had obtained it, not suspecting that the second lane had come from an experiment of his own. Elmer WD at 62; Tr. at 993.[74] He testified that Dr. Angelides led him to believe that someone else (either Mark Lewallen or someone from Dr. Waxman's laboratory) had obtained these results, and that he only learned differently after reviewing his own research records during the Baylor investigation. Id.

Additional support for the conclusion that Dr. Angelides was responsible for the preparation of the substitute figure supplied for the Glia paper comes from reviewing the records and testimony relating to Medical Illustrations file 150319. Hearing Ex. 43. This file was opened by Dr. Angelides on May 31, 1989 (during the interim period between when Dr. Angelides indicated he was preparing a new figure from a "different experiment" and when the Glia paper was finally accepted). A bill to Dr. Angelides is included in the file, dated June 6, 1989, for three prints with an extra charge for rush work. The file contains a variety of negatives and prints of the lanes used in the Glia figure alone and in combinations. It is difficult to ascertain precisely which items were the subject of Dr. Angelides's original request, unfortunately, because the file folder indicates four subsequent requests for reprints in 1994 apparently in relation to the Baylor investigation. Dr. Gilbert testified that, when he and Dr. Berget first examined this file on behalf of the Baylor Sub-Committee, the contents included a photograph of the Glia figure and three other photographs, each of which had a lane cut out which proved to correlate with one of the lanes used in the final figure. Gilbert WD at 47. Dr. Gilbert explained that the Sub-Committee then requested photographs to be made of these cut-out photographs which were used to make comparisons with the original source data (Dr. Elmer's Olmsted Western blot, Dr. Wood's silver-stained gel and Dr. Wood's Mab3 blot). Id. at 46.

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[74]When asked before the Baylor Sub-Committee why he thought he was listed as a co-author on the Glia paper when he did not believe that the Western blot data included in the paper were his, Dr. Elmer explained that he had believed it was because he developed the antibody that was used in the paper. Ang. Ex. 98, at 144-45.

The Panel found Dr. Gilbert's testimony on this subject credible. His description of the original contents of the Medical Illustrations file and the series of reprints requested by the Sub-Committee for purposes of comparison with the final figure was consistent with the file as it now exists (despite the absence of a documentary trail sufficient to independently establish each step now). Dr. Angelides offered no explanation as to why he would have requested prints made of any of the contents of the file in May 1989 other than in relation to the preparation of this figure. Further, Dr. Gilbert's testimony before the Panel was consistent with the Baylor Report which he co-signed and Dr. Angelides offered no reason why Dr. Gilbert would have benefited from misrepresenting the contents of the file during the Baylor investigation. Baylor Report at 130-31.

c. Intentionality of the misrepresentation of the data in Figure 1 of the Glia paper

The Panel found the evolution of Figure 1 of this paper particularly compelling evidence that Dr. Angelides acted intentionally in fabricating and misrepresenting the data presented in it. After the initial submission of the manuscript, Dr. Angelides wrote to Dr. Elmer expressing the intention to replace the existing Figure 1 (which had been recycled from the PRSL paper) with new data, purportedly because his principles would be violated by reusing already-published data. ORI Ex. 90A. The figure which Dr. Angelides then submitted to Glia consisted of different lanes drawn from the primary data sources identical to those which were found to be the source of the lanes used in the PRSL/ANYAS figure. These two sources, as discussed above, were experiments found in the records of Dr. Elmer and Dr. Wood, both of whom had left his laboratory months before the Glia paper was submitted. It is extremely difficult to see how different portions of the same two distinct primary data sources drawn on for the PRSL/ANYAS figure could have been selected <u>accidentally</u> to represent new experimental data again using optic nerve. In order to find the different lanes, the drafter would have had to view the original data sources and not simply have relied (as Dr. Angelides had claimed in relation to PRSL) on removing a figure created by Dr. Elmer for an earlier draft manuscript. On their face, the original data sources contained sufficient notations to have, at the least, alerted Dr. Angelides that experiments of different researchers were involved and that the molecular weight species in the immunoblot lane was not recorded as 260 kDa. In addition, the primary data were clearly labeled as to the purity of the antigen in a manner not consistent with the claim that the antibody was being tested against crude glycoproteins.[75] Dr. Angelides did not offer any evidence that he sought assistance from Dr. Elmer at that point to explain or clarify the inconsistencies that would have been apparent when the primary data sources were revisited to create this new figure.

Dr. Angelides suggested that perhaps the large work included in early draft manuscripts contained inadvertent errors that "got propagated in all sorts of different directions," so that the different versions could have become the figures for the PRSL/ANYAS and the GLIA papers.

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[75]The primary data indicate that the antigen used in that lane was "DEAE-WGA fraction," whereas the two right-hand lanes were simply labeled as crude glycoproteins. Even if Dr. Angelides mistook the glycoproteins involved as rat optic nerve rather rat brain, the notation "DEAE-WGA" meant that the antigen had been partially purified. Elmer WD at 18.

Tr. at 1913-14. He acknowledged that the Glia figure was sent to the Yale collaborators long after Dr. Elmer was gone, but claimed that photographs of optic nerve data that were not used in the Brain Research paper as it evolved were utilized in the Glia paper. Id. Dr. Angelides offered no plausible scenario for how he obtained photographs and selected the lanes used here and presented them as showing a 260 kDa band detected by 7493 antibody in optic nerve glycoproteins, in the absence of Dr. Elmer and with no labeling on the data or photographs to support these representations. He showed no example of any pre-existing versions of this figure prepared while Dr. Elmer was present to demonstrate that he might have merely propagated errors or misinterpretations originally caused by Dr. Elmer.

In addition, Dr. Angelides asserted that Dr. Elmer and he together "wrote the figure legend that referred to Lanes 1, 2, and 3" of Figure 1 in the Glia paper. Tr. at 1650. Dr. Elmer flatly denied this. Tr. at 2024. Dr. Angelides never explained when and how Dr. Elmer could have participated in writing this figure legend. The language of the figure legends (while presenting the data as coming from the same kind of experiments) is entirely different in the PRSL, ANYAS, and Glia paper figures. Hence, an independent drafting process had to have occurred to create the figure and legend supplied to Dr. Black in May 1989, rather than a simple carry-over of text language that might have propagated erroneous assertions from the first publications to the others. Conscious intervention was necessary to prepare the new figure using different lanes of data and describing the experiments in different language.

The Panel concluded that the fabrication and falsification of Figure 1 of the Glia paper was an intentional act and that Dr. Angelides is the person responsible for that intentional act.

d. Conclusion regarding Figure 1 of the Glia paper

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the presentation of data in Figure 1 of the Glia paper. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides intentionally falsified the figure by misrepresenting the experiments from which the data were drawn, misrepresenting the molecular weight of the immunoreactive band in the second lane of the figure, misrepresenting the purity of the antigen tested in lane 2, and misrepresenting the tissue source of the proteins tested as optic nerve. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive and that the conduct proven constituted scientific misconduct.

3. Figure 1 of the PNAS papers

The PNAS paper focused on sodium channels in rat sciatic nerve rather than optic nerve tissue. Antibody 7493 was again used, as one method of studying the localization of sodium channels in Schwann cells within adult rat sciatic nerve. The abstract of the paper highlights the claim that antibody 7493 "specifically recognizes a 260-kDa protein corresponding to the á subunit of the sodium channel in immunoblots of crude glycoproteins from rat sciatic nerve." PNAS paper at

9290. This claim is documented by Figure 1 which purports to be an "immunoblot analysis of antibody 7493 immunoreactivity in rat sciatic nerve." PNAS paper at 9291. The first lane is again a silver-stained gel reported to be of rat sciatic nerve glycoproteins. Id. The second and third lanes are reported to have been loaded with 800 µg of rat sciatic nerve glycoproteins,[76] but no explicit assertion is made that the proteins were derived from the gel shown in the first lane.[77] Id. The second lane purports to show 7493 specifically recognizing a 260-kDa protein while the third lane shows no immunoreactivity with pre-immune serum. Id. Again, ORI charged that the figure was intentionally falsified, in that the antibody used was not 7493 and the antigen was not rat sciatic nerve. ORI Findings # 4C, at 47-48.

a. Primary data for the lanes in Figure 1 of the PNAS paper

Dr. Wood recognized the silver-stained gel in the first lane as derived from another lane in the same data used in the PRSL, ANYAS and Glia figures. Wood WD at 26-27. The protocol for his November 30, 1988 experiment identifies the corresponding tissue loaded in that lane only as peripheral nerve. Hearing Ex. 8, at 86. Since the source of the peripheral nerve tissue could be rat sciatic nerve, no falsification was charged in regard to the tissue source of the first lane of this figure. See ORI Findings, ¶356, at 45.7

The second and third lanes were identified in data from an experiment of Dr. Elmer's dated April 8, 1988. Hearing Ex. 26. The tissue source for all lanes in that experiment is identified on the primary data as "crude synaptosomal GP [glycoproteins]." Id. Dr. Angelides acknowledged that synaptosomes, which are prepared from brain synapses, cannot be derived from sciatic nerve. Ang. Br. at 204; Elmer WD at 26-27, 72-73. Further, lane 2, represented as showing 7493

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[76]Dr. Wood testified that he never had enough sciatic nerve glycoproteins to load 800 µgs on two lanes and that, in any case, the two immunoblot lanes did not come from his experiment. Wood WD at 26-28.

[77]ORI admitted that, unlike the ANYAS/PRSL and Glia figure legends, the PNAS figure legend does not explicitly state that lanes 2 and 3 were performed using eluted material from lane 1, ORI Br. at 82, n. 71, but ORI nevertheless argued that this conclusion was supported by the testimony of Dr. Patrick. Patrick WD at 27; see also Gilbert WD at 52-54. ORI listed a finding that such a claim was made, but did not include it as a numbered charge in its charge letter. The allegation that this constituted an instance of misconduct per se did not arise until ORI's post-hearing brief. Dr. Angelides generally disputed this finding in his initial response to the charge letter, but did not specifically address it in his testimony or his briefs. Neither ORI expert indicated what particular circumstances or words supported their opinion, and the Panel has determined that the legend and text are ambiguous in this respect. The Panel also determined that the manner in which ORI raised this issue -- as a finding rather than as a charge -- did not give Dr. Angelides sufficient notice that the Panel was being asked to rely on this item as a separate instance of scientific misconduct. Consequently, the Panel did not rely on this finding in its analysis of PNAS Figure 1.

antibody, is identified in the primary data as showing mAb3 monoclonal antibody, and Dr. Angelides agreed that the representation of this lane was erroneous. Ang. Br. at 203-204.

b. Responsibility for the creation and publication of Figure 1 of the PNAS paper

Dr. Elmer testified that he was not aware of the publication of the PNAS paper until the Baylor investigation. Elmer WD at 11, 71. He testified that he never received drafts, galley proofs, or reprints of this manuscript. Id. at 71. This testimony is consistent with the fact that he is not listed as a co-author on the paper. Dr. Elmer further testified that he was "not involved with the preparation of this figure at any time" and did not select the lanes from his data or describe them as showing sciatic nerve. Id. at 72; see also Tr. at 2024-25 (Elmer).

Dr. Angelides asserted that his "recollection of the creation of this figure was that it was already prepared by the time Dr. Elmer had left the laboratory" and that it was prepared by Dr. Elmer and himself. Tr. at 1452. He testified that Dr. Elmer had conducted the experiments on sciatic nerve, and that the data had been photographed, cut into strips and assembled into a publication-ready figure before Dr. Elmer's departure. Tr. at 1452-53. Dr. Angelides testified that he believed in good faith at the time that lane 2 showed sciatic nerve glycoproteins probed with 7493 antibody. Id. at 1453-54. He agreed that the lane was actually probed with monoclonal antibody mAb3, but believes this error was inadvertently propagated from an earlier version of the figure. Id. He stated that he is not now certain if lanes 2 and 3 were actually rat brain rather than sciatic nerve glycoproteins. Tr. at 1454. However, he argued that he relied on the representations in Dr. Elmer's publication-ready figure. Ang. Br. at 204.

Based on the evidence in the record, the Panel did not find plausible Dr. Angelides's claim that he relied in good faith on a pre-existing publication-ready figure prepared by Dr. Elmer before he left the laboratory. Dr. Angelides produced no such pre-existing figure matching Figure 1 of the PNAS paper. No such figure was located in Dr. Elmer's records or in his thesis. The original primary data, labeled inconsistently with the way it is used in the PNAS figure, remained in Dr. Elmer's records. It is unlikely that Dr. Elmer would prepare a figure falsely representing the tissue source in this experiment and provide it to the head of his laboratory and then retain the contradictory primary data in records which he was leaving with the laboratory head.

In addition, while there was no evidence to support Dr. Angelides's allegation that Dr. Elmer constructed a final figure matching the presentation of data in PNAS, there was evidence that Dr. Angelides requested photographs and reprints from the Medical Illustrations facility of the figure in final form. See ORI Ex. 49 (Medical Illustrations file 157727). The initial request in this file was by Dr. Angelides and was dated January 30, 1990; Dr. Angelides ordered reprints

on March 28, 1990. ORI Ex. 49, at 1-3. The PNAS paper was submitted in May 1990. The file contains the final three-lane figure. ORI Ex. 49, at 7, 10; Record Ex. 1, at Enc. II.C.4.11. As with the Medical Illustrations file relating to the Glia figure, it is difficult now to reconstruct the original contents since prints were also ordered in 1993 and 1994 in relation with the Baylor investigation. Dr. Gilbert testified that the Sub-Committee used the data from the Medical Illustrations file to construct a composite with the lane at issue from the primary data in order to verify the identity of the lane by visual comparison. Gilbert WD at 55; Record Ex. 1, at Enc. II.C.4.17. However, he testified that the final figure constructed for PNAS was in the original file. Gilbert WD at 55. For the same reason discussed in relation to the Medical Illustrations file relating to the Glia figure, the Panel found Dr. Gilbert's testimony on this point credible. The Panel concluded that Dr. Angelides had access to the primary data and obtained prints of the constructed figure in final form and at a time consistent with his having prepared the figure for the PNAS paper, which was well after the experimentalists had left the laboratory.[78]

c. Intentionality of the misrepresentation of the data in Figure 1 of the PNAS paper

Dr. Angelides was again the sole author from his laboratory listed on this paper, and no other acknowledgment was made that Dr. Wood or Dr. Elmer contributed data to the paper. As to this paper, Dr. Angelides testified that he "distinctly remember[ed]" that he had asked that Dr. Elmer's name be included but that Dr. Waxman had demurred because he considered that Dr. Elmer had "received sufficient mileage out . . . of the preparation of the 7493 antibody not to have been included on this paper." Tr. at 1458 (Angelides). Dr. Angelides stated that he did not "take issue with him at all" about this. Id. Despite this attribution of responsibility for the omission of Dr. Elmer to Dr. Waxman, the Panel considers Dr. Angelides ultimately responsible for the accuracy of the presentation of data from his laboratory, since he provided the data without insisting on acknowledging its source. No evidence was presented to indicate that the other co-authors would have had any way to know which laboratory members had conducted the experiments that produced the specific data (as opposed to their general awareness that Dr. Elmer originally created the reagent).

Further, the primary data from which lane 2 of Figure 1 in the PNAS paper was drawn was also included in 1989 draft manuscript versions of what later became the Brain Research paper. ORI Ex. 7; Hearing Ex. 11. Lane 3 of Figure 1C of that draft manuscript is identical to lane 2 of the PNAS figure, but is represented in these manuscripts as probing partially purified sodium channel with "affinity purified anti-260 kDa specific" antibody. ORI Ex. 7, at 43, 56; ORI Ex. 40, at 28, 35; Hearing Ex. 11, at 26 (figure legend). Dr. Elmer testified that he never obtained

[78]Dr. Angelides disputed the significance of the Medical Illustrations file evidence on the grounds that the presence of a final figure in the file undercuts the claim that the file demonstrated his construction of the PNAS figure or contained the component data from which the lanes used were extracted. See Ang. Br. at 155-56. The relevance of the Medical Illustrations file, however, is not to track the creation of the figure from the component data sets but to document further Dr. Angelides's direct role in the production of the final figure.

any anti-260 kDa specific antibody. Elmer WD at 20, 43, 73. The use of the same data misrepresented in a different, equally false, way in earlier manuscripts makes it more likely that the misrepresentation of the data in the PNAS paper as sciatic nerve probed with 7493 antibody was an intentional act.

Dr. Elmer testified that he had specifically discussed with Dr. Angelides the Western blot from which the lanes used in this figure were drawn, because the experiment was performed after the adoption of the protease inhibitor cocktail and resulted in "the best data" he obtained using 7493 with crude synaptosomal glycoproteins. Elmer WD at 74. For this reason, Dr. Elmer believed Dr. Angelides was aware of these experimental results and knew that they did not involve rat sciatic nerve. Id. The fact that these data were significant results that had been expressly drawn to Dr. Angelides's attention by the experimentalist additionally makes it more likely that the misrepresentation of the tissue source was intentional.

In addition, Dr. Elmer testified, and the Panel confirmed, that a review of his records did not show any Western blot data using 7493 antibody to probe sciatic nerve proteins. Elmer WD at 27; Hearing Exs. 14, 15, and 51. The absence of such data is further corroborated by the fact that Dr. Elmer did not report results with sciatic nerve among the tissue sources probed with 7493 in his thesis. See Hearing Ex. 25, at Figure 5-3. It is more likely that the misrepresentation of the tissue source was intentional since no alternative accurate results were available.

Dr. Angelides argued that ORI failed to show that the errors in the figure were material to the paper. Ang. Br. at 201-04. However, Dr. Waxman testified that Figure 1 was important to the paper as a whole because it demonstrated the specificity of the 7493 antibody in sciatic nerve tissue to a protein of the correct size for the sodium channel of interest. Waxman WD at 15. This testimony about the role of the data in Figure 1 in substantiating the interpretation of the other data presented in the paper was corroborated by Drs. Black, Gilbert and Patrick. Black WD at 9-10; Gilbert WD at 51-52; Patrick WD at 28. Dr. Angelides minimized the importance of Figure 1 to the paper but acknowledged that, if the immunoblot lane in Figure 1 was performed with a monoclonal antibody, a "disconnect" would exist with the rest of the paper showing immunoelectron microscopy using a different antibody (7493). Ang. Br. at 209. The disconnect is particularly troubling in light of Dr. Black's testimony that the monoclonal antibodies were not useful for electron microscopy. Black WD at 7. Dr. Angelides also pointed to the reference in the PNAS paper to the Brain Research paper then listed as "in press" (see footnote reference 13 in the PNAS paper), as providing sufficient information on the properties of the antibodies. Ang. Br. at 203. Of course, this reference can only provide a circular argument for Dr. Angelides, in that the data presented in Brain Research are also alleged to be falsified. Dr. Angelides further argued that ORI failed to provide evidence that "inclusion of the immunoblot of figure 1 contributed to a favorable review" in the form of a referee's report. Ang. Br. at 209. Dr. Angelides pointed to no standard or requirement that the materiality of a misrepresentation and the consequent motivation to make such a misrepresentation can only be demonstrated by a reviewer highlighting the particular item of data that was falsified in a review of the publication involved, and the Panel found no basis to impose such a requirement. Furthermore, Dr. Black

testified, as a co-author and scientist with experience publishing in this field, that "without Western blot data in those papers, they never would have been accepted, that this was an antibody that had not been characterized in the published literature. Having said that, we would feel very uncomfortable with the interpretation if we didn't have supporting Western blot data to bolster the notion that this particular antibody is recognizing a particular molecular weight species." Tr. at 1935. The Panel concluded that the data in Figure 1 were material to the PNAS paper and that Dr. Angelides had a motive to intentional falsify the figure, lacking legitimate immunoblot data showing 7493 specifically recognizing a 260 kDa protein in sciatic nerve tissue.

d. Additional Arguments offered by Dr. Angelides on this issue

Dr. Angelides argued that Dr. Elmer's testimony about not having performed a Western blot with 7493 against sciatic nerve was not credible because he was confused about his own data due to the passage of time and the disorganization of his records. Ang. Br. at 161, n.131; Tr. at 1750-51. Further, Dr. Angelides argued that Dr. Elmer's testimony about sciatic nerve experimentation was conflicting, in that before the Baylor Sub-Committee he stated that he definitely "did sciatic nerve" but did not remember ever having done optic nerve. Ang. Br. at 208. The reference to Dr. Elmer's testimony does not indicate what experiments he actually performed with sciatic nerve or whether they yielded useful results. In his testimony before the Panel, Dr. Elmer stated that he may have done experiments with 7493 and sciatic nerve but found no Western blot data that could correspond to the figure here. Elmer WD at 75. He further testified that he did not remember obtaining any Western blot with 7493 against either optic or sciatic nerve tissue extracts. Tr. at 2025. Dr. Elmer had not had the opportunity to review all his research records before he was questioned at Baylor but did have that opportunity before his testimony in this case, so it is not surprising that his testimony would be more specific. See Elmer WD at 66. An independent review of Dr. Elmer's records corroborates that no experiments are recorded with optic nerve and that, despite some notations about sciatic nerve, no data or records indicate that Dr. Elmer ever obtained a Western blot with 7493 against sciatic nerve glycoproteins. In any case, the crucial issue is not whether Dr. Elmer ever conducted experiments with sciatic nerve but whether the experimental data reported in the PNAS figure 1 were sciatic nerve data as claimed. On this point, Dr. Elmer is clear that they were not, and he is corroborated by the well-labeled primary data. See Elmer WD at 72-75; Hearing Ex. 26.

Dr. Angelides further argued that the absence of data on sciatic nerve in Dr. Elmer's records (as reported by Drs. Gilbert and Patrick) ought to be disregarded. He argued that Drs. Gilbert and Patrick admitted "they did not review any primary data or Dr. Elmer's notes" so their review was "disparate and incomplete." Ang. Br. at 207. Dr. Angelides has mischaracterized these scientists' testimony and, in any event, the Panel ascertained based on its own review of the record that no such data existed.

Dr. Angelides argued that Drs. Waxman and Black were not credible as experts because they had demonstrated bias against him by their actions in 1997 in retracting articles published with Dr. Angelides, including the PNAS paper, without seeking Dr. Angelides's consent. Ang. Br. at 14-

15. Dr. Angelides argued that he would have been eager to correct the errors that have been found but that he was denied this opportunity by the unilateral action of his co-authors. Ang. Br. at 209. Drs. Black and Waxman testified that Dr. Angelides never suggested making any corrections or retractions of the four papers (unlike the Corrigendum proposed by Dr. Angelides for the Brain Research paper discussed below). Black WD at 20; Tr. at 1928 (Black); Waxman at 32. The co-authors testified that they took unilateral action to withdraw the PNAS paper only after being informed that ORI had found that Dr. Angelides committed scientific misconduct in relation to those papers. Id.; Tr. at 1949-50 (Black).[79] The retractions disclosed that Dr. Angelides contested Baylor's findings in a civil lawsuit and had appealed ORI's charges against him, but stated that the listed co-authors nevertheless could not stand behind the papers in light of the ORI findings. Hearing Ex. 48; see also ORI Ex. 89 (Brain Research retraction). The Panel appreciates that it would have been preferable for the co-authors to have requested Dr. Angelides's participation in informing the scientific public that these papers contained errors, even though they could have expected, from his behavior with respect to the proposed Corrigendum to the Brain Research paper (discussed further below) and his challenges to Baylor's and ORI's findings, that Dr. Angelides would not acquiesce to retraction. The Panel does not conclude that the co-authors' conduct indicates a bias that impugns their expert status. Moreover, the co-authors were cited as experts by ORI principally for their opinions on the materiality of the falsifications to the papers' central findings. As explained above, the Panel determined from the papers themselves that the co-authors' views were correct.

e. Conclusion regarding Figure 1 of the PNAS paper

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the presentation of data in Figure 1 of the PNAS paper. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides intentionally falsified the figure by misrepresenting the antibody used in the second lane of the figure and misrepresenting the tissue source of the proteins tested in lanes two and three as sciatic nerve. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive and that the conduct proven constituted scientific misconduct.

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[79]Dr. Black acknowledged that the retraction of PNAS was published in the Brain Research journal, after PNAS declined to publish it without the participation of all the co-authors. Tr. at 1928, 1949-50. Drs. Black and Elmer indicated that the publication of their retraction in Brain Research instead of PNAS was an "embarrassment" and "surprise" to them. Tr. at 1950 (Black); Tr. at 2056 (Elmer). Dr. Waxman indicated that the reason he felt it necessary to publish the retraction was to "protect the integrity of the scientific literature" in light of the questions raised about the 7493 antibody data in the findings against Dr. Angelides. Waxman WD at 32. Dr. Black testified that Dr. Angelides was not requested to join in the retractions because the Yale co-authors did not believe he would cooperate. Tr. at 1928, 1949 (Black).

4. Overall Conclusion Regarding Falsifications in four Yale Papers

The Panel concluded that Dr. Angelides intentionally falsified and misrepresented the data in Figure 1 of each of the four papers described above in which he collaborated with co-authors from Yale University. In addition to the specific evidence as to each paper discussed in detail above, the Panel's conclusion was further supported by its observation of several patterns in the misuse of the data in these papers.

First, data drawn from a single experiment were often used for multiple inconsistent purposes in different papers. Such multiple inconsistent usage suggests that Dr. Angelides returned to the original data sources to construct each figure and made conscious decisions about how to present the lanes from the data in each instance, reducing the possibility that an inadvertent error was propagated through later reuse of a figure.

Second, in at least three of the four papers, lanes in the figures purporting to represent data from one experiment were actually derived from completely unrelated experiments. The experiments involved were performed at different times, using different reagents, and by different experimentalists. Even in the PNAS paper, where no explicit claim of a single experiment was made, the same practice occurred of combining data from completely unrelated experiments from different researchers and different time frames without indicating this in the paper. Further, this pattern did not merely reflect the repetition of a single error because the papers used different lanes of Dr. Wood's silver-stained gel and tied them to two entirely different experiments of Dr. Elmer's. In neither case had Dr. Elmer prepared any silver-stained gel in relation to his experiment, minimizing any possibility of simply confusing gels. In no case did either of the scientists perform joint experiments or work together to generate the data and neither had any explanation for how the data of one became intermingled with data generated by the other.

Third, Dr. Angelides did not seek the assistance of the scientists who did the experiments in identifying and interpreting the data or preparing them for publication. In each case, Dr. Angelides published results that were represented in a manner not supported on the face of the primary data after the experimentalist had left his laboratory. Nevertheless, Dr. Angelides has not shown any evidence, despite his acknowledgment that it would be standard practice to do so, that he either communicated with the experimentalists to be sure of the accuracy of his representations about their data or involved them in reviewing the actual presentation of their data in the manuscript preparation process.

Fourth, Dr. Angelides failed to acknowledge fully the contributions of the experimentalists in these papers. Dr. Angelides did not include Dr. Wood as an author or acknowledge his contribution in any of the papers although his data appeared in every one. Dr. Elmer was listed as an author in only two of the four papers, although all of them contained his data and were based on the use of the 7493 antibody that he developed. This pattern of excluding the experimentalist from authorship suggests that Dr. Angelides sought to avoid the possibility that the experimentalist would recognize and object to or correct misrepresentations of the data.

The Panel found the recurrence of these patterns of behavior by Dr. Angelides in preparing these four papers over the course of more than two years to be compelling evidence of intentional misconduct and lack of integrity.

C. The Brain Research Paper

Dr. Angelides was co-author of an article detailing the characterization of the monoclonal (mAb1 and mAb3) and polyclonal (7493) antibodies against rat brain sodium channel in 1990, "The voltage-dependent sodium channel in mammalian CNS and PNS: antibody characterization and immunocytochemical localization," 532 Brain Research 222-231 (1990), in Record Ex. 1, at Enc. II.C.4.30 (Brain Research paper). Dr. Elmer was the first author on the Brain Research paper, which was accepted on May 15, 1990. Id. Drs. Black and Waxman contributed electron microscopy data and were also listed as co-authors. Much of the material in the Brain Research paper is related to research also reported as Chapter 5 of Dr. Elmer's doctoral thesis. Hearing Ex. 25.

The Brain Research paper reports that all three antibodies immunoblot a 260 kDa polypeptide and are able to recognize the á subunit of the sodium channel in both central and peripheral nervous system neurons (but not skeletal or cardiac muscle). Brain Research paper at 222-23. These assertions are documented in two figures which allegedly contain falsified data. Figure 2A purported to show immunoblot data of polyclonal and monoclonal antibodies reacting only with a species of 260 kDa molecular weight in crude synaptosomal glycoproteins. ORI charged that Figure 2A was falsified in that the proteins probed in the immunoblot lanes did not come from the gel of crude glycoproteins shown in the first lane but instead were purified sodium channel proteins, and that this falsification enhanced the apparent ability of the antibodies to detect the á subunit of the sodium channel in a complex mixture of proteins. Figure 3 was a 12-lane figure that purported to demonstrate specificity of the polyclonal (lanes 1-8, 11, and 12) and monoclonal (lanes 9 and 10) antibodies against various tissues. ORI charged that Figure 3 was falsified in several respects. First, the prominent band in lanes 1-4 is identified as at 260 kDa, whereas the primary data labeled the band as 180 kDa. Second, the antigen was incorrectly reported for three lanes (4, 10, and 12). Third, the antibody used in lanes 9 and 11 was mAb1, not, as reported, mAb3 or 7493 respectively. We address below first the charges relating to Figure 2A and then those relating to Figure 3.

1. Figure 2A of the Brain Research paper

Figure 2A presents six lanes of data demonstrating the immunoreactivity of the polyclonal and monoclonal antibodies against crude rat brain membrane glycoproteins. Brain Research paper at 224.[80] The first lane purports to be a silver-stained gel of rat brain synaptosomal glycoproteins. Lanes 2-6 purport to show those glycoproteins transferred to nitrocellulose and probed with, in order, 7493 antibody, affinity-purified 7493 antibody, preimmune 7493 antisera, mAb1 supernatant, and mAb3 supernatant. No reactivity was evident in the lane probed with preimmune antisera. The remaining immunoblot lanes each showed a single band with an assigned molecular weight of approximately 260 kDa. Dr. Angelides was charged with intentionally falsifying the purity of the antigen. ORI Findings # 4D, at 51.

Dr. Angelides acknowledged that the antigen was actually purified sodium channel, not crude glycoproteins, but attributed this misstatement to "an error in the assembly of this manuscript, in which we had, Dr. Elmer had prepared prints of what ultimately became Figure 2A." Tr. at 1361. He contended that the error was not attributable to him but rather to Dr. Elmer, who participated in preparing the manuscript through a series of drafts during which errors somehow occurred and were propagated years after. Ang. Br. at 216-19.

a. Primary data for the lanes in Figure 2A of the Brain Research paper

The primary data for lanes 2-6 were located in a Western blot with the date of April 11, 1988 in Dr. Elmer's records. Record Ex. 1, at Enc. II.C.4.32. Notations on the primary data identified the antibodies used as 7493 and the monoclonals, corresponding to their presentation in the figure. However, the antigen is labeled in the primary data as "purified á subunit." The same five lanes from this Western blot are also presented in Dr. Elmer's thesis figure 5-2 as lanes 8-12, but there they are identified as testing the antibodies against purified sodium channel, consistent with the notation on the primary data. Lane 7 in the thesis figure presented silver-stained gel data, as did lane 1 in the Brain Research paper figure, but the gel lane was not the same as that used in the figure in the paper. The parties did not locate the original data for the silver-stained gel lanes, but Dr. Elmer testified that the lane presented in the paper showed a complex pattern consistent with crude glycoproteins, whereas the lane in the thesis appeared to be a stain of the purified sodium channel proteins. Elmer WD at 46, 50.

b. Responsibility for the creation and publication of Figure 2A of the Brain Research paper

Although he agreed that the data shown in lanes 2-6 of the figure were from his experimental data, Dr. Elmer denied that he prepared Figure 2A for publication as it appeared in the final Brain Research paper. Elmer WD at 34, 47-48. Dr. Elmer asserted that he did not review manuscripts

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[80]The legend to the figure implies but does not state that the glycoproteins tested were a crude mixture, but the text of the paper referencing this figure explicitly states that the Western blot analysis was run on "crude membrane glycoproteins." Brain Research paper at 226.

for the Brain Research paper after October 1988 and that earlier drafts that he did review did not contain the falsified data. Id. at 34-48.[81]

In testifying before the Baylor Sub-Committee, Dr. Elmer initially thought it possible that the misstatement about the purity of the antigen in Figure 2A was merely the result of an accidental switch of legends with Figure 2B, which did use crude glycoproteins. See Ang. Ex. 98, at 151-54; Baylor Report at 141. However, Dr. Angelides acknowledged before the Panel that (as was pointed out in the Baylor Report) such an accidental switch could not have caused the error because Figure 2A existed and was incorrectly described in drafts of what became the Brain Research paper prior to the inclusion of Figure 2B. See Ang. Br. at 218-19; cf. Baylor Report at 141. Instead, he argued that the mislabeling was propagated from an earlier manuscript version of the figure which was at one time reviewed by Dr. Elmer. Ang. Br. at 217-18. Thus, Dr. Angelides argued that Dr. Elmer copied the erroneous presentation of Figure 2A from Figure 1B in a manuscript draft dated October 7, 1988 which bore the word processing designation "Voltage.KJA." Ang. Br. at 217; Record Ex. 43, at 268-69. However, the draft to which Dr. Angelides cited does not contain any figures, but only the text of figure legends, so that it is not possible to reach the conclusion he suggested based on a review of that draft. Further, Dr. Angelides did not provide evidence that any earlier draft reviewed by Dr. Elmer contained an actual figure with the same primary data described as using crude glycoproteins. The only draft versions which contained the figure itself, with the lanes erroneously identified as in Figure 2A, were dated in 1989 or later. See ORI Exs. 7, 40. By that time, Dr. Elmer had left the laboratory and completed the defense of his thesis, leaving his primary data with Dr. Angelides. Dr. Angelides offered no credible evidence that Dr. Elmer participated in reviewing drafts of the manuscripts prepared after his departure or that Dr. Elmer returned to the laboratory in order to check the presentation of data in the figures against his primary data. Dr. Angelides does not dispute that the thesis and the draft manuscript diverged after Dr. Elmer left the laboratory. Ang. Br. at 140.

The Panel found compelling the evidence that Dr. Angelides was responsible for the presentation of data in the Brain Research figure, that Dr. Elmer presented the data in his thesis in a manner entirely consistent with the notations on his primary data, and that the erroneous identification of the data occurred only after Dr. Elmer left the laboratory.

c. Intentionality of the misrepresentation of the data in Figure 2A of the Brain Research paper

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[81]Dr. Angelides claimed that Dr. Elmer admitted at the hearing that he wrote some of the figure legends, contradicting the understanding of the Baylor Sub-Committee. Ang. Br. at 165. Dr. Angelides misstated Dr. Elmer's testimony. Dr. Elmer testified, consistent with the Baylor Report and the evidence before the Panel, that legends in early versions of the writing that evolved into Chapter 5 of his thesis and the Brain Research paper were in his own handwriting but that later versions in which the figures became expanded contained Dr. Angelides's writing and not his own. Tr. at 2056-57 (Elmer).

The Panel found it unlikely that the misrepresentation of the purity of the antigen occurred by unintentional error. First, as discussed above, the primary data for the immunoblot lanes were clearly labeled as using purified sodium channel and were presented as such in Dr. Elmer's thesis, with which Dr. Angelides was heavily involved and which he ultimately approved. Hearing Ex. 25; Hearing Ex. 51; Record Ex. 1, at Enc. II.C.4.32; Elmer WD at 29-31. After reviewing the primary data, Dr. Angelides's own expert witness, Dr. Pfenninger, agreed that the representations about lanes 2-6 of Figure 2A of the Brain Research paper and the representations about lanes 8-12 of Thesis Figure 5-2 were in conflict and that the thesis figure was the one that corresponded to the primary data. Tr. at 619-620. Given Dr. Angelides's active role in preparing both the thesis and the paper and his continuous access to the primary data, the Panel found it unlikely that he would not notice the conflict.

Second, the use of a different silver-stained gel lane in Figure 2A, particularly one that enhances the false impression that the antibody was more rigorously tested by using crude instead of purified proteins, is telling evidence that the falsification of the purity of antigen was intentional. Dr. Elmer testified that lane 1 in the Brain Research paper figure appeared, on its face, to be a complex mixture of proteins consistent with the claim in the legend that the associated immunoblot lanes were run against crude glycoproteins. Elmer WD at 46, 51. By contrast, Dr. Elmer pointed out that the silver-stained gel lane included in the thesis figure clearly "shows a predominant protein that marks the position of the sodium channel subunit in the purified preparations." Id. at 46. The difference in the complexity of the protein mixtures shown in the silver-stained lanes in Figure 2A and the thesis figure was visible on review by the Panel as well. The use of a silver-stained gel lane representing crude glycoproteins (which could not have been the gel lane from which the purified proteins tested in the primary data were in fact taken) required conscious effort. While the source of the silver-stained gel has not been identified, clearly the creation of this figure (as with the figures in the four Yale papers discussed above) required combining data from unrelated experiments. The choice of this particular silver-stained data, as Dr. Elmer testified, had the effect of making it appear more plausible, as claimed in the legend, that "the data in lanes 2-6 of Figure 2A [were] generated as a Western blot of a crude glycoprotein extract, when it was really done using a purified sodium channel preparation." Id. at 46-47.

Third, the order in which the immunoblot lanes are presented in the thesis figure is precisely the same as that in which they appear in the raw data. Compare Hearing Ex. 25, at figure 5-2, with Hearing Ex. 51. By contrast, the lanes in Figure 2A are presented in a different order. The alteration in the order of the lanes in the final figure from that in the primary data and the thesis figure further demonstrates that Figure 2A required conscious effort to assemble, so that it is unlikely that an error was simply propagated into the final figure.

Fourth, the misrepresentation of the purity of the antigen was material because it tended to enhance the presentation of the specificity of the antibodies in the paper. Dr. Angelides himself recognized that Figure 2A was significant in that it "attempted to show that the sodium channel antibodies reacted with a prominent band at or near 260 kDa that corresponded to the alpha

subunit of the sodium channel." Ang. Br. at 210. However, he argued that the erroneous claim that a complex rather than purified protein mixture was used to demonstrate specificity was not important. Id. He relied on testimony by Dr. Pfenninger to assert that an antibody's specificity can be demonstrated in either crude or purified protein. Id. Dr. Pfenninger, however, also testified that he would not misrepresent which was used. Tr. at 616. Furthermore, Dr. Angelides's other expert witness, Dr. Limbird, testified that the more rigorous challenge to test an antibody's ability to identify a specific protein is to "[a]pply it against a crude mixture." Limbird WD at 6 (emphasis in original). Furthermore, Dr. Elmer, who was performing the actual experiments, testified that the results he was able to obtain with purified proteins differed substantially from those he was able to obtain with crude glycoproteins, in which he was never able to obtain a single band at 260 kDa using antibody 7493. Elmer WD at 21-22. Dr. Elmer's testimony was in accord with the results of the Panel's independent review of his records. Thus, regardless of whether either approach might, as a general matter, be useful in determining specificity of an antibody, it is clear that in this case the data were not interchangeable. Scientific readers were entitled to accurate information on which to assess how specifically the antibody would perform in identifying the á subunit alone in complex protein mixtures.

Dr. Angelides also asserted that the errors in reporting the purity of the antigen used were immaterial on the grounds that other independent tests establish the specificity of the antibody. Ang. Br. at 211. He cited to Dr. Limbird's testimony that there was evidence in the primary data demonstrating specificity of 7493 for sodium channel. Ang. Br. at 211; Limbird WD at 3. The charges against Dr. Angelides do not rest on a claim that the 7493 antibody does not recognize the á subunit or is not specific for the sodium channel. The charges rest on whether Dr. Angelides knowingly misrepresented particular data. That the misrepresentations tended to enhance the perceived degree of specificity of the antibody for particular uses is relevant to explaining his motivation in considering whether the admitted misstatements were likely to have been made intentionally. Nevertheless, no scientist, apart from Dr. Angelides, who appeared before this Panel suggested that it would be acceptable to alter the identification of data in a published paper merely because a researcher believed that other data that might support the ultimate conclusion of the paper were available.

d. Additional Arguments offered by Dr. Angelides on this issue

Dr. Angelides argued that he should not be penalized for misstatements in the Brain Research paper, since he tried to correct the errors in a Corrigendum but was thwarted by the lack of cooperation of the co-authors. Thus, he argued that he did all that a responsible researcher could do to correct the scientific record, once he learned of mistakes. Ang. Br. at 212; ORI Ex. 85. The record does not support Dr. Angelides's assertions.

On November 23, 1993, the Baylor Sub-Committee sent Dr. Angelides a letter specifically extending its investigation to address questions about the Brain Research paper. Ang. Ex. 15. Drs. Waxman and Black testified that Dr. Angelides contacted them in December 1993 about correcting some minor "typographical errors" that he said he had discovered; Dr. Angelides

expressly denied to them that any allegations of misconduct had been raised concerning the Brain Research paper. Black WD at 15; Waxman WD at 26.

Dr. Elmer testified that Dr. Angelides also contacted him in late November or early December of 1993 and said that "some problems with the Brain Research paper . . . had been uncovered by the Baylor Sub-Committee during its investigation" that he wished to discuss with Dr. Elmer. Elmer WD at 55. Dr. Elmer testified that Dr. Angelides then flew to Detroit and met with Dr. Elmer at the airport and explained that the legends to Figures 2A and 2B had been switched, in addition to identifying problems with the presentation of data in Figure 3 (discussed below). Dr. Elmer stated that Dr. Angelides prepared, and Dr. Elmer agreed to join in, a draft Corrigendum during the airport meeting, but that Dr. Angelides told him that the Corrigendum should not include all the identified errors (in particular, the misstatement of the molecular weight of the antigen bands in lanes 1-4 of Figure 3 and an inaccurate description of the derivation of the monoclonal antibodies) because the editor of Brain Research might then object to publishing the correction. Id. at 56-57.[82]

On December 19, 1993, Drs. Black and Waxman received a copy of a Corrigendum which had already been submitted without their review to the editor of Brain Research on December 12, 1993. However, the editor of Brain Research declined to publish the Corrigendum absent the signatures of all co-authors, and the Yale co-authors insisted on approval from Baylor before signing. ORI Exs. 86, 87. After the Baylor Sub-Committee and ORI found that data in the paper had been falsified, Drs. Elmer, Waxman and Black joined in retracting the paper. ORI Ex. 89. All three co-authors testified to these events in a manner consistent with each other and contradicting Dr. Angelides's account.

Dr. Angelides's conduct in relation to the Corrigendum is consistent with an awareness of having misrepresented data in the Brain Research paper and an effort to further conceal the extent of the falsifications, rather than with his claim of having made every reasonable effort to correct errors in the scientific record that he had himself discovered.

Dr. Angelides also argued that ORI's charges were premised on a scenario whereby Dr. Angelides falsified Figure 2A by removing lane 7 (the silver-stained gel) from Dr. Elmer's thesis and preparing a falsified figure with new silver-stained gel using the Medical Illustrations facility. Ang. Br. at 213. Dr. Angelides asserted that this scenario, supported by the testimony of Drs. Patrick and Gilbert, was "reckless," because Figure 2A of the Brain Research paper was not derived from the same photographic prints used in the thesis figure, and because the Medical

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[82]Dr. Elmer testified that at the time he accepted Dr. Angelides's guidance about the scope of the correction, but that, ultimately, he concluded that Dr. Angelides sought to submit a limited Corrigendum in order to deflect the inquiry into the charges at Baylor and to retain the appearance of honest error, as opposed to intentional falsification. Elmer WD at 57-59.

Illustrations files do not demonstrate that Dr. Angelides constructed Figure 2A by altering the thesis figure to remove lane 7 and substitute a new silver-stained lane. Ang. Br. at 213-16.[83]

Dr. Angelides mistakes the significance of the use of different silver-stained gel lanes in the presentation of the immunoblot data in Figure 2A of the paper and thesis figure 5-2. Our conclusion that the misrepresentation in the paper that the antibodies were tested against crude glycoproteins was most likely to have been made intentionally is supported by the use of a different silver-stained gel lane, especially one specifically consistent with the claim that a complex mixture of glycoproteins was the source of the antigen used in the immunoblot lanes. Our conclusion is further supported by the presentation of the same data elsewhere (i.e., in Dr. Elmer's thesis) in a way consistent with the notations on the primary data as to antigen and in association with a silver-stained gel lane consistent with the presentation of purified protein.

Dr. Angelides's scenario is not relevant to our conclusions. It is evident on the face of the two figures that the paper presents a silver-stained gel lane that enhances the plausibility that crude glycoproteins were tested, while the same immunoblot data are presented in the thesis in association with a silver-stained gel lane consistent with the notations in the primary data indicating that purified protein was used. It does not matter whether the thesis figure or the primary data or an earlier version of the figure were used in the physical process of constructing the figure for the paper. The fact that the immunoblot data were joined in the paper to a lane of silver-stained gel with which they could not have been associated experimentally increases the likelihood that the purity of the antigen was falsified intentionally rather than misstated by error. The Panel relied on the evidence relating to the Medical Illustrations files only to the extent that it supported Dr. Angelides's access to the data at issue and the absence of any involvement by Dr. Elmer in production of figures after the fall of 1988.

Dr. Angelides also asserted that there was no reason to misrepresent the data presented in Figure 2A, because Dr. Elmer conducted numerous successful experiments producing legitimate data of the same kind. Ang. Br. at 211-12. Dr. Elmer, however, testified that he never obtained results similar to those presented in Figure 2A using antibody 7493 against crude glycoproteins. Elmer WD at 46-47. Dr. Angelides did not produce a legitimate experiment with results that could have been used for the presentation made in Figure 2A, i.e., 7493 recognizing a single band at a molecular weight of 260 kDa in crude glycoproteins. Dr. Angelides suggested that other data

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[83]Dr. Angelides also suggested that, because Dr. Elmer's thesis was not bound until April 1989, Dr. Angelides did not have it available until well after a version of the paper that became Brain Research was submitted to another journal and that version already contained the data that were published in Brain Research. Ang. Resp. to Baylor Report at 80. Therefore, Dr. Angelides contended he could not have altered the data from the thesis in producing the Brain Research paper. Id. This contention is misplaced. Clearly, Dr. Angelides had reviewed and approved Dr. Elmer's thesis long before it was bound. More importantly, no particular significance attaches to whether he removed the data from the thesis to alter them or used the original primary data that he had retained in the laboratory during this period.

were once available in Dr. Elmer's records that could have been used, but that such data were now missing either because Dr. Elmer did not maintain thorough records or because of losses after their confiscation by the Baylor Sub-Committee. Ang. R. Br. at 197-98. Although Dr. Angelides repeatedly suggested that data supportive of his claims might be missing from Dr. Elmer's records, Dr. Elmer himself testified that the extant records contain virtually all the significant results from his experiments. Elmer WD at 5.[84] As noted above, Dr. Elmer also said he never got such conclusive results, so there is no reason to believe that any lost data would have supported Dr. Angelides's claims. The Panel found that, while Dr. Elmer's records were not well-organized, they correlated closely with his descriptions of the experimental work and provided adequate information to support generally the testimony that he offered about his results. Therefore, the Panel found that Dr. Elmer's testimony about his work was credibly corroborated by his records. The absence of available and legitimate alternative data is further support for the Panel's conclusion that the misrepresentation of the data in Figure 2A was intentional.

e. Conclusion on Figure 2A of the Brain Research paper

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the presentation of data in Figure 2A of the Brain Research paper. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides intentionally falsified the figure by misrepresenting the purity of the antigen against which the antibodies were tested. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive and that the conduct proven constituted scientific misconduct.

2. Figure 3 of the Brain Research paper

Figure 3 of the Brain Research paper presented a panel of immunoblots testing the polyclonal and monoclonal antibodies against 12 different tissues. Brain Research paper at 225. The text explains the purpose of the figure as showing an analysis to determine the tissue specificity of the antibodies. Id. at 227-28. The left portion of the figure shows eight lanes (1-8) run on 3-12% gel using polyclonal antibody 7493 against the following tissue sources: lane 1--rat whole brain; lane 2--mouse whole brain; lane 3--rat P3 synaptic membranes; lane 4--rat sciatic nerve; lane 5--rat skeletal muscle; lane 6--rat cardiac muscle; lane 7--rat liver; and lane 8--rat testes. The paper reported that lanes 5-8 showed no evidence of immunoreactivity and these data are not challenged. Lanes 1-4, however, were reported to show the antibody recognizing a 260-kDa peptide in the tissues listed. ORI alleged that the prominent bands shown in lanes 1-4 were

[84]Dr. Elmer testified that after a close review he found the following: "I have records of most of my experiments, at least the ones that were significant or positive. Furthermore, my records are representative of the experiments I performed. If any data are missing, it is likely that the results were not positive or significant. I believe that my records accurately describe the experiments performed." Elmer WD at 5.

actually at 180 kDa, according to a review of the primary data, and that lane 4 was not run against rat sciatic nerve, as claimed, but rather brain tissue. ORI Findings # 4E, at 56.

The right portion of the figure shows four lanes run on 4-15% gel testing monoclonal antibody mAb3 against rat brain (lane 9) and rat sciatic nerve (lane 10) and testing polyclonal antibody 7493 against spinal cord neurons (lane 11) and dorsal root ganglia (lane 12). ORI alleged that the tissue sources in lanes 10-12 were misrepresented and were in fact rat brain glycoproteins. ORI Findings # 4E, at 56. In addition, ORI charged that the antibody in lanes 9 and 11 was mAb1, rather than mAb3 or 7493, as presented. Id.

Dr. Angelides acknowledged that Figure 3 contained errors but denied that he was responsible for the errors. Ang. Br. at 234. He denied that the molecular weight of the bands in lanes 1-4 was 180 kDa and asserted that the molecular weight was properly assigned at the time the manuscripts were drafted. Id. at 227-28, 231. He denied that the antigens in lanes 10-12 were mislabeled. Id. at 234. He admitted that the antigen was wrongly identified as sciatic nerve in lane 4 and that the antibodies in lanes 9 and 11 were mislabeled. Id. He contended that the errors occurred unintentionally during the process in which Dr. Elmer and he together drafted manuscripts that became incorporated into both the Brain Research paper and Dr. Elmer's thesis. Id. Dr. Angelides claimed that Dr. Elmer became confused about the primary data and kept poor records, but that Dr. Elmer, unlike Mr. Lewallen and Dr. Wible, did not "intentionally mislabel" his own data. See Ang. Resp. to Baylor Report at 65; Ang. Br. at 128-29, 131; Tr. at 1460-61, 1750-51.

a. Primary data for the lanes in Figure 3 of the Brain Research paper

The primary data for lanes 1-4 of Figure 3 were located in Dr. Elmer's records in a data array of nine lanes of immunoblot lanes. Record Ex. 1, at Enc. II.C.4.41; original in Hearing Ex. 51. The first three lanes of the figure were lanes 3, 4 and 5 respectively from the left in the original primary data; the fourth lane of the figure was the right-most (ninth) lane in the primary data. On the far left of the array of original primary data, notations of molecular weights at 180 and 250 were pencilled in. Each lane in the figure contained a prominent band that was lined up at the same height. However, in the primary data, these bands were at somewhat different heights, but all appeared close to the height of the 150 kDa molecular weight notation and none of the prominent bands was close to the 260 kDa notation. Lanes 3-5 in the primary data are identified as 7493 antisera against rat whole brain, mouse whole brain, and rat P3 synaptosomes respectively, and the corresponding lanes 1-3 in the figure were described consistently with those identifications. However, lane 9 in the primary data is identified as 7493 against P3 synaptosomes, whereas lane 4 of the figure is described as testing sciatic nerve.

The primary data for lanes 9-12 of Figure 3 were also located in Dr. Elmer's records in a different array of Western blot data consisting of two panels. Record Ex. 1, at Enc. II.C.4.42. The primary data identified the antibody tested in each lane but had no notation as to the antigen used. The first lane of the first panel was presented as lane 9 of the figure where it was described

as mAb3 tested against rat brain. The primary data show the antibody used in the first lane of the first panel as mAb1, not mAb3. The second lane of the first panel was presented as lane 10 of the figure where it was described as mAb3 tested against rat sciatic nerve, which was the same as the antibody identified in the primary data. The first lane of the second panel was presented as lane 11 of the figure where it was described as 7493 tested against spinal cord neurons. The primary data show the antibody tested in that lane as mAb1, not 7493. Finally, the last lane of the first panel is presented as lane 12 of the figure where it was described as 7493 tested against dorsal root ganglion. Thus, the antibodies noted as used in two of these lanes in the figure (9 and 11) were not consistent with the notations on the primary data.

As stated, the antigen used in lanes 9-12 of the figure is not noted on the original primary data. However, Dr. Elmer testified that he performed these antibody tests against rat brain glycoproteins except where specifically noted otherwise. Elmer WD at 28-29, 54-55. He specifically testified that each of the lanes shown in the primary data was run against rat brain. Id. at 28-29. Thus, the antigens noted as used in three of these lanes in the figure (10-12) were not consistent with the experimentalist's testimony as to the antigen used and were not supported by any labeling on the primary data.

b. Responsibility for and intentionality of the misrepresentation of the data in Figure 3 of the Brain Research paper

Much of the discussion in regard to Figure 2A about the process by which Dr. Elmer's thesis and the Brain Research paper drafts diverged and Dr. Angelides's exclusion of Dr. Elmer from the latter stages of the drafting process during which misrepresentations of the data became incorporated in the manuscript also applies to the Panel's evaluation of whether Dr. Elmer or Dr. Angelides is responsible for the final presentation in Figure 3, and we rely on that analysis here as well. Once again, the Panel found no evidence of misidentification of the data in what became Figure 3 of the Brain Research paper in any version of the manuscript before Dr. Elmer left the laboratory and completed his thesis. The same data were presented in Dr. Elmer's thesis in Figure 5-3 in a manner consistent with the labeled primary data. A careful review of the documentary record, including all the extant drafts, corroborated Dr. Elmer's testimony that the presentation of data did not diverge from the identification shown on the primary data until after Dr. Elmer completed work on his thesis.[85] Dr. Angelides alone had access to both Dr. Elmer's

[85]Dr. Angelides placed emphasis on earlier drafts that reference Western blot data on PNS tissue, but none of these drafts contained any actual data. Rather, the references were contained in legends for proposed figures. Ang. Br. at 221-22; see, e.g. Ang. Ex. 10, at Bates-numbered page 16591 et seq.; Record Ex. 43, at 268-69, ORI Ex. 79, at 34-35. The Panel did not conclude that the language in these legends contradicted Dr. Elmer's testimony or proved that Dr. Elmer "approved" the false claims made in the Brain Research paper, since, at the time of those drafts, Dr. Elmer may have planned to complete experiments that could have provided additional data by the time that any figure was prepared for publication. Dr. Angelides produced no version of

(continued...)

thesis and Dr. Elmer's primary data when Dr. Angelides was preparing the Brain Research paper for submission after Dr. Elmer's departure. This chronology is consistent with intentional falsification of the data by Dr. Angelides.

Dr. Elmer testified that the lanes in the primary data used in lanes 1-4 of the figure in the paper were from experiments he ran in June and July 1987, before he had obtained an optimal protease inhibitor cocktail. Elmer WD at 27-28. At that point, he was never able to obtain a single band at the 260 kDa weight with the 7493 antibody. Id. at 21-28. Furthermore, Dr. Elmer testified that he specifically discussed the June/July 1987 experimental data from which lanes 1-4 were drawn with Dr. Angelides and that Dr. Angelides never disagreed with Dr. Elmer's determination that the molecular weight was approximately 180 kDa. Id. at 25-26; Tr. at 2035-36 (Elmer). Dr. Elmer testified that, if he had successfully obtained a prominent 260 kDa in the summer of 1987, he would not have continued, as he did, to pursue that goal and would have gone on to other experiments. Tr. at 2035-36. The Panel found that it is not plausible that Dr. Angelides was unaware that the molecular weight of the prominent band in lanes 1-4 was represented inaccurately, since his attention had been drawn to these particular experimental results as showing the persistent problem with 7493 reacting most strongly with a species of lower molecular weight than expected.

Unlike Dr. Elmer's thesis, the Brain Research paper contained no textual discussion alerting readers to the occurrence of a band with a molecular weight of approximately 180 kDa in immunoblots run with the polyclonal antibody.[86] Had such a discussion been included, the likelihood that the errors in identifying data in the figures were the result of intentional falsification would have been reduced. However, not only was such a discussion omitted but, in fact, it was included in earlier drafts while Dr. Elmer was still in the laboratory but then removed from the final published version. See, e.g., Ang. Ex. 43, at A-248-49. Dr. Angelides attributed the removal of the discussion to editing by Drs. Black and Waxman. Ang. Resp. to Baylor Report at 78-79. However, they denied making this change and it is unlikely that they would have done so unilaterally since the data were generated in Dr. Angelides's laboratory. Waxman WD at 23-24. The removal of this language from the text supports the Panel's conclusion that

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[85](...continued)
the paper or thesis chapter 5 dated prior to December 1988 that contained erroneously-labeled data.

[86]In the thesis, Dr. Elmer wrote that in crude glycoproteins and purified sodium channel, 7493 reacted with a major band at 260 kDa but also sometimes recognized proteins at 180 kDa and 60 kDa to varying degrees. Hearing Ex. 25, at 117-18. The 180 kDa protein was reported to be highly antigenic and likely to be a proteolytic breakdown product of the sodium channel detectable at all stages of purification but only faintly visible in final sodium channel fractions. Id. The thesis reported that the monoclonal antibodies did not react with the 180 kDa protein. Id. at 119.

Dr. Angelides intentionally falsified Figure 3 to enhance the impression that 7493 specifically bound only to the á subunit of the sodium channel.

After reviewing the other lanes included in the primary data arrays, the Panel determined that none of the primary data arrays identified as the source of any of the immunoblot data in the figure was labeled as derived from testing of PNS tissue. Consequently, the misrepresentation of the antigen source was unlikely to have resulted from simple error, such as selecting the wrong lane from the original data array to show results with PNS-derived antigens. Furthermore, Dr. Elmer testified that he did not repeat a tissue specificity screening experiment like that from which lanes 1-4 were derived. Elmer WD at 27-29; Tr. at 2036. Before January 1988, Dr. Elmer testified that he had not optimized the protease inhibitor cocktail and was not obtaining prominent bands above 200 kDa with 7493. Elmer WD at 16-17, 22; Tr. at 2060-61. After that date, he testified that he did additional Western blots but generally used brain glycoproteins as the antigen, except in a few instances that were clearly labeled in the primary data, and that he did not conduct additional comparisons across tissue sources. Elmer WD at 27-29, 54-55; Tr. at 2031, 2035-36. Dr. Elmer testified that he never led Dr. Angelides to believe that he had Western blot data using 7493 or the monoclonal antibodies that would show them binding to the 260 kDa sodium channel in PNS tissues, in particular sciatic nerve tissue. Tr. at 1001-02, 2025-31; 2040-41 (Elmer). Dr. Angelides was not able to produce any such Western blot data. As with Dr. Angelides's claims that data supportive of his claims in Figure 2A may have once existed but are now missing from Dr. Elmer's records, the Panel found nothing in reviewing Dr. Elmer's records that would suggest that data supportive of Dr. Angelides's claims in regard to Figure 3 had been removed. The absence of alternative legitimate data that could have been used in place of the erroneously-labeled data in Figure 3 further suggests that the mislabeling was intentional.

Furthermore, the Panel found that the misrepresentations of molecular weight and tissue source in Figure 3 were important to the paper as a whole. The main impact of the alterations of the data was to create the impression that: (1) antibody 7493 consistently recognized a single protein of the anticipated molecular weight of the intact á subunit of the sodium channel, and (2) antibody 7493 was able to recognize that protein in both CNS and PNS tissues. In fact, as discussed above, the evidence shows that 7493 was not reacting prominently to a 260 kDa protein in the data shown and did not consistently do so in the laboratory at the time, but rather reacted as well with a protein of about 180 kDa, which may or may not have been a proteolytic breakdown product. Further, the evidence shows that no legitimate data supported the claim that 7493 behaved as reported with PNS tissues. In each case, these misrepresentations enhanced the

paper's claims for the specificity and utility of the 7493 antibody. Therefore, Dr. Angelides had a motive to present these data falsely.[87]

The misidentifications of the antibodies in lanes 9 and 11 were less clearly central to the purpose of the paper. The effect of changing the antibody used in lane 11 from mAb1 in the original data to 7493 was to give the appearance that 7493 produced a single prominent band of high molecular weight, as did the monoclonal antibodies, when that was not the case, so that alteration did contribute to the thrust of the paper's claims as to the characterization of 7493. The alteration of the monoclonal antibody in lane 9 from mAb1 in the original data to mAb3 was less significant, but did result in a better total presentation in the figure. Thus, lanes 9-12, which are grouped together, are presented as showing a single monoclonal antibody (mAb3) tested against CNS (lane 9) and PNS (lane 10) tissues followed by the polyclonal antibody (7493) tested against PNS (lane 12) and CNS (lane 11) tissues. Accurately reporting that lane 9 used a different antibody than lane 10 would have somewhat weakened the force of the comparison. In any case, the antibodies used are clearly labeled on the primary data. Had the misidentification of the antibodies been the only misstatement in the paper, the Panel might have been less certain that it represented an intentional effort to mislead. In the full context of the misrepresentations in both figures of this paper, however, the Panel concluded that Dr. Angelides acted intentionally in misreporting these data.

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[87]Dr. Angelides further supported his claim that he had no particular motive to demonstrate a comparison between CNS and PNS reactivity by asserting that the initial interpretation by both Dr. Elmer and himself was that 7493 was reactive with sodium channel in neurons but not in glial cells. Ang. Br. at 163-64. He argued that revisions were made in the drafts of the manuscript because later data did not support this interpretation, not in order to enhance the acceptability of the manuscript. Id. The reviewer's report on the earlier version of the manuscript that became the Brain Research paper (but which was submitted to and rejected by the Journal of Biological Chemistry in May 1989) confirms that its claim that the antibodies are highly specific in central and peripheral neurons but not in muscle or glial cells requires "significant additional experimentation." Record Ex. 43, at Att. II.27, at A325. The referee accepts as clearly supported, however, the claim that the á subunit is recognized in peripheral neurons as well as brain based specifically on the data in lane 4 (which Dr. Angelides admitted and we have found was run on CNS not PNS tissue). Id. at p. A326. We find that the fact that Dr. Angelides and Dr. Elmer at some point believed that the antibodies were unreactive in glial cells but later changed their interpretation does not in any way reduce Dr. Angelides's motive to strengthen the support for the claim that 7493 was able to recognize the á subunit in PNS as well as CNS tissue, and, if anything, the referee's report on the rejected draft adds to the evidence on that motive.

c. Additional Arguments offered by Dr. Angelides on this issue

Dr. Angelides argued that ORI distorted the meaning of the Brain Research paper by reading into it a comparison between the immunoreactivity of the antibodies in CNS and PNS tissues. Ang. Br. at 221-22. An independent reading of the paper makes clear that its focus is on the characterization of the antibodies, and that the ability of the antibodies to recognize the á subunit of the sodium channel in both CNS and PNS tissue is highlighted in the title, abstract, and text, as well as in the data presented in the figure at issue. See, e.g., Brain Research paper at 222, 223, 225, 228. In addition to the Panel's own assessment of the importance of the PNS data in Figure 3 to the paper, ample evidence and testimony in the record confirmed that the absence of valid PNS data in Figure 3 would, as Dr. Angelides's own expert testified, undercut a central point of the paper in establishing the capacity of the antibody to react with specificity with sodium channels in CNS and PNS tissue but not skeletal or muscular tissue. Tr. at 657. (Pfenninger). The other authors of the Brain Research paper testified that the demonstration in Figure 3 of the immunoreactivity of the antibodies in both CNS and PNS tissue was very important in the paper as a whole. See Black WD at 14-15; Tr. at 1942-43 (Black); Waxman WD at 21; Elmer WD at 45, 47, 51. Dr. Elmer also testified that at the time that the Brain Research paper was published, "[o]ther scientists in the sodium channel field, such as Dr. Catterall, had developed antibodies that recognized the sodium channel only in extracts from the central nervous system. Thus, it would have been significant to report that the 7493 and monoclonal antibodies recognized a sodium channel protein in the peripheral nervous system as well as brain." Elmer WD at 51; see also Tr. at 662 (Pfenninger). The Panel found that the demonstration that 7493 was specific for sodium channel in PNS tissue as well as CNS tissue, as documented in Figure 3, was material to the paper's favorable presentation of the antibody as a "unique" tool, and, therefore, that Dr. Angelides had a motive to misrepresent the data presented in Figure 3. Cf. Brain Research paper at 222.

Dr. Angelides also argued that any error in the presentation of the immunoblot data was insignificant in light of other unchallenged data in the paper and elsewhere that independently established 7493's specificity for sodium channels within PNS tissue. Ang. Br. at 226. The experimentalists who performed the immunostaining with 7493 on PNS tissue denied that their data independently established the specificity of 7493 for sodium channels in those tissues. On the contrary, Dr. Black testified that the interpretation of electron microscopic staining data presented in the Brain Research paper depended on the evidence for the specificity of the 7493

antibody presented in Figures 2A and 3. Black WD at 15.[88] The immunostaining data thus could not substitute for valid data in those figures.

Dr. Angelides argued that it was improper for the Baylor Sub-Committee and ORI to assign a molecular weight to lanes 1-4 because the lanes came from gels run at different times and under different conditions. Ang. Br. at 229. He asserted that, for that reason, the authors consciously chose not to include molecular weight markers in the figure. Tr. at 1313-18 (Angelides). While the figure itself does not show molecular weight markers, the text clearly states that the molecular weight of the peptide recognized by the antibodies in lanes 1-4 is 260 kDa. Brain Research paper at 225, 228. The prominent bands in these lanes are presented as lined up at roughly the same height. In particular, the bands in the first four lanes had to be moved in order to line up the bands so closely, since in the primary data array they are shown as aligned more loosely around the 180 kDa level. The contemporaneous molecular weight notations made by the experimentalist on the composite array of the primary data that he prepared are more credible

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[88]Dr. Angelides presented testimony that he freely shared reagents from his laboratory, including the polyclonal antibody 7493, with other researchers, implying that he would have been unlikely to do so had he intentionally misrepresented the characteristics of the antibodies in the Brain Research paper. See, e.g., Tr. at 1607-08 (Angelides); Devor WD at 4, 8-9; Epstein WD at 4-5, 11-12; Ang. Ex. 7. The Panel concluded for several reasons that Dr. Angelides's willingness to share the 7493 antibody with other researchers does not in itself refute the evidence that he was aware that some of the data he published concerning the reagent were false. First, many of the recipients of the antibodies, like Drs. Black and Waxman, were likely to have intended to use them as reagents for further study, such as ultrastructural localization, relying on the published characterization of the antibodies by Dr. Angelides's laboratory, rather than themselves testing specificity directly. See, e.g, Black WD at 14-15; Devor WD at 9-10; Benke WD at 8-10. Second, even were the recipients' results to be less successful than those reported by Dr. Angelides, differences in antigen preparation or other conditions could have explained the differences in results in different experiments in different laboratories, given the history of difficulties Dr. Elmer had in optimizing conditions. See, e.g., Tr. at 601-02 (Pfenninger). In fact, some recipients testified that they did not find the same specificity in their laboratories as that claimed by Dr. Angelides in the Brain Research paper. Dr. Pfenninger, for example, testified that he would not publish a claim that 7493 recognized only a single prominent band of 260 kDa based on the results achieved with 7493 in immunoblots in his laboratory. Tr. at 603. Dr. Benke testified that a collaborator tried to verify the claimed specificity of 7493 for sodium channel and found that it "did not show binding to a protein with a molecular weight greater than 200 kDa using rodent brain preparations" even though a commercially-available reagent was able to identify such a protein in the same preparations. Benke WD at 9. However, the charges against Dr. Angelides are not founded on allegations that 7493 does not recognize sodium channels but rather on allegations that Dr. Angelides falsified data in order to make a stronger case for 7493's ability to specifically bind to sodium channels in particular tissues than could be supported by the legitimate data available in his laboratory at the time. Simply providing the reagent to collaborators would not necessarily have risked exposing such falsification.

than Dr. Angelides's present claim (contradicted by Dr. Elmer) that he and Dr. Elmer agreed on the 260 kDa claim at the time the figure was prepared. The Panel concluded that the paper asserted a false claim that the prominent bands in lanes 1-4 were at the 260 kDa molecular weight, that the data were intentionally manipulated to create this impression, and that the claim was not supported by any primary data.

Dr. Angelides denied that the antigen in lanes 10-12 was wrongly presented and that it should have been rat brain. Ang. Br. at 233-39. Dr. Angelides argued that ORI merely made an unfounded assumption that any unlabeled lane in a Western blot should be labeled ten years after the fact as rat brain, whereas the contemporaneous assignment of antigen (which he alleged he made together with Dr. Elmer) should actually be accepted as more current and therefore more accurate. Id. at 233-34. The Panel did not find this argument persuasive. It is true, as noted above, that the primary data for lanes 10-12 are not identified as tested against rat brain. However, it is equally true that there are no notations on the primary data to support Dr. Angelides's claim that the antigens were rat sciatic nerve, spinal cord neurons, or dorsal root ganglion respectively. The testimony of the researcher who conducted the experiment that his practice was to use rat brain (synaptosomal membrane glycoprotein fractions) in these tests, and to note the antigen when he varied from this practice, contradicts Dr. Angelides's position. Elmer WD at 27-29, 54-55. Dr. Elmer's description of his practice was corroborated by the Panel's review of his data records. His thesis described his preparation of brain membrane glycoproteins for use in immunoblots. Hearing Ex. 25, at 105. In addition to his testimony about his general practice, Dr. Elmer explained that the purpose of the experiment from which these lanes were drawn was to screen the rabbit anti-peptide antibodies with which he was working at the time for specificity against the sodium channel using the monoclonal and polyclonal antibodies as positive controls. Elmer WD at 28-29. For that purpose, he used a single antigen (rat brain glycoproteins) and varied the antibody in each lane; to have used different tissue sources in each lane would have invalidated the intended comparison among the antibodies. Id. Dr. Elmer's testimony about the nature of the experiment was credible and consistent with the data.

Dr. Angelides again attacked ORI's use of Medical Illustrations records to attribute to him responsibility for the preparation of Figure 3. Ang. Br. at 236-38. He denied that the creation of the figure in final form could be traced through the Medical Illustrations files cited by the Baylor Sub-Committee for that purpose. Id.; Baylor Report at 154-55; but see ORI Br. at 70-72. Although the Panel examined the Medical Illustrations files at issue, the conclusion that Dr. Angelides was responsible for intentionally falsifying Figure 3 is amply supported by the evidence in the record discussed above even without any reliance on the contents of those files. It is difficult for the Panel to reach final resolution as to whether the construction of the figure can be tracked through the files without testimony identifying and interpreting the written instructions, orders, and photographic output and without the submission of the original files themselves in order to review legible copies of prints and negatives. In addition, as noted elsewhere, it is unfortunate that the Baylor Sub-Committee made requests for reprints that were retained in the same files, making it problematic to determine the precise state of the files before

the investigation. However, it is clear from the order forms and files that at least some data which Dr. Angelides acknowledges to be those used in Figure 3 are present in files from which Dr. Angelides was making orders well after Dr. Elmer's departure. Certainly, nothing in the Medical Illustrations files demonstrates any involvement by Dr. Elmer in creating the final figures.

Dr. Angelides also contended that Dr. Elmer once shared the interpretation that his data showed immunoreactivity of 7493 in PNS tissues because he included such claims in his own handwriting in a draft of what became the Brain Research paper, and because the title of his thesis still references PNS. See Ang R. Br. at 196; Tr. at 1333-34, 1336-37. The handwritten draft to which Dr. Angelides referred does contain a statement that "[in] Western blot analysis, the affinity purified antibodies reacted with central, peripheral and sensory nervous tissue." Record Ex. 43, at Att. II.14, page A-139. However, the writing appears to a very rough, presumably early draft and, in any event, contains no data or details to support a claim that data had been produced at that point. The thesis title may reflect work other than the immunoblotting at issue here or may have been carried over without correction from earlier drafts. It is possible that further experimentation was intended or anticipated at some point, but no testimony or evidence that these claims about PNS were ever substantiated was provided in this proceeding.[89] In any case, the essential point is that the charges on Figure 3 are based on false representations about primary data that does exist and that clearly are not consistent with the claims made in the Brain Research paper. For that purpose, it is not critical to establish that no Western blot data using 7493 against PNS tissues ever existed.

Dr. Angelides also contended that he was not aware of the errors in the Brain Research paper and that others who "carefully reviewed" the manuscript failed to alert him to any problem. Ang.

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[89]Dr. Elmer testified that he never told Dr. Angelides that he had obtained a Western blot of 7493 against dorsal root ganglion (DRG). Tr. at 2031. He also testified that he did not remember ever performing such an experiment and had not located any such data. Tr. at 2040. Further, he testified that the only evidence that 7493 reacted with PNS tissue was based on immunocytochemical studies with DRG neurons (but not Western blots). Tr. at 1003-04, 2040. However, Dr. Elmer's thesis states that 7493 has previously been shown to be specific in Western blots of yDRGs. Hearing Ex. 25, at 159. ORI explained the discrepancy by arguing that the thesis sentence is incorrect and possibly attributable to Dr. Angelides's involvement in drafting the thesis. ORI Br. at 73, n.59. Since Dr. Elmer testified before us that he did not do the experiment and offered no data to support the statement in his thesis, we find that his statement against his own interest is likely to be credible. In any case, responsibility for the admittedly-inaccurate statement in Dr. Elmer's thesis is not at issue in the present matter. Ultimately, regardless of whether any data were ever produced probing dorsal root ganglions with 7493 on a Western blot, the data presented as such in the Brain Research paper are still in existence and clearly did not involve dorsal root ganglion.

Response to ORI Charge Letter, Tab A at 50. Specifically, he alleged that Mr. Lewallen worked closely with a manuscript version of the Brain Research paper in performing experiments to complete the paper and, at the same time, worked with Dr. Elmer's thesis, and yet did not identify any discrepancies to Dr. Angelides. Id. Mr. Lewallen testified that Dr. Angelides asked him in August 1989, in a handwritten memorandum to which Dr. Angelides attached a draft paper, to complete some experiments with the antibodies. Lewallen WD at 48; ORI Ex. 7. He testified that he was never given a copy of Dr. Elmer's thesis. Lewallen WD at 48-49. Furthermore, although some of his experimental data appeared in the published paper, Mr. Lewallen testified that he was not told that the manuscript was being submitted, he did not put his data into a figure for the paper, nor was he ever given an opportunity to review the presentation of his data before publication. Id. at 50-51. Mr. Lewallen was not included as an author on the published paper, although his contribution of data for Figure 2 was acknowledged. There is thus no evidence that Mr. Lewallen had any opportunity or reason to compare the presentation of Dr. Elmer's data in the draft paper with either Dr. Elmer's thesis or primary data.

Dr. Angelides has also attributed responsibility to Drs. Black and Waxman for failing to bring any errors in data presentation in the Brain Research paper to his attention, since they had possession of Dr. Elmer's thesis. Ang. Resp. to Baylor Rep. at 79. However, even were the Yale co-authors to have noticed discrepancies between the descriptions of data in figures presented in the paper and the thesis, they had no access to the primary data to determine that the same experiments were being used for both purposes. Further, it is not evident why they would undertake such a comparison, since the immunoblot data were not the area in which they were contributing to the paper. Both Drs. Black and Waxman testified that they did not view this as their responsibility but rather relied on Drs. Elmer and Angelides to ensure the accuracy of data contributed from Dr. Angelides's laboratory. Black WD at 14; Waxman WD at 22-23. Drs. Black and Waxman would have had no way to verify the presentation of the data against the original primary data.

Dr. Angelides also argued that Dr. Elmer never alerted him to any inaccuracies in the Brain Research (or other papers) and therefore shared responsibility for any "pattern of carelessness." Ang. Br. at 165. Given the Panel's findings that the falsifications of data occurred after Dr. Elmer had left the laboratory and that he was not provided with an opportunity to review the later drafts containing the falsifications before the Brain Research paper was submitted (and was not even aware of its submission), it is difficult to see how Dr. Elmer would have been likely to suspect that the data were not accurately presented. This is particularly so since he did not have ready access to his own primary data to check against the published figures. Nevertheless, Dr. Elmer bears and has acknowledged responsibility for failing to more "carefully inspect this paper after it was published." Tr. at 2054. Dr. Angelides also contended that Dr. Elmer had participated in the preparation of the Corrigendum without suggesting that the molecular weight assigned in lanes 1-4 of Figure 3 should be corrected. Ang. Br. at 232. As discussed above,

Dr. Elmer testified that he proposed precisely that, and that Dr. Angelides refused the suggestion on the grounds that the editor of the journal would object to too many corrections. Elmer WD at 56-58.

Dr. Angelides's position that all the co-authors should share equal responsibility for the errors in the paper is not reasonable where the other co-authors would have no reason to suspect or means to detect intentional falsification by him. Cf. Ang. Br. at 124. In any case, whether any of the other co-authors could or should have detected the falsification of the data in Figure 3 is ultimately irrelevant to the Panel's conclusion that Dr. Angelides himself intentionally chose to present the data falsely.

d. Conclusion on Figure 3 of the Brain Research paper

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the presentation of data in Figure 3 of the Brain Research paper. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides intentionally falsified the figure by misrepresenting the molecular weight of the reactive species in the first four lanes, the identity of the antibodies used in lanes 9 and 11, and the tissue source of the antigen used in lanes 4, 10 and 12. The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive and that the conduct proven constituted scientific misconduct.

3. Overall Conclusion Regarding falsifications in the Brain Research

The Panel concluded that Dr. Angelides intentionally falsified and misrepresented the data in Figures 2A and 3 of the Brain Research paper for the reasons explained in detail above. In addition to the specific evidence as to falsification of data in each figure, the Panel's conclusion was further supported by several overarching considerations.

First, the Panel found that Dr. Angelides's failure to seek Dr. Elmer's active participation in the later stages of preparation of the Brain Research paper was further evidence that Dr. Angelides acted intentionally in misrepresenting the data. This conclusion was particularly compelling in light of the substantial differences in data presentation in the draft manuscripts after Dr. Elmer had ceased to be involved. Dr. Elmer's testimony that he was not sent manuscripts to review before their submission (and in some instances was not even informed that papers had been submitted) was corroborated by the experience of other researchers working with Dr. Angelides who reported that they were not shown copies of the final versions of manuscripts submitted with their names as authors. See, e.g., Wible WD at 6 (Dr. Angelides submitted paper with her name to Neuron after her departure from laboratory and without her knowledge); Tr. at 808-13, 847-49 (Dr. Wood never saw abstract submitted in his name containing false statement at ORI Ex. 56); see also Tr. at 893-94, 2057 (Dr. Elmer also never saw manuscript submitted to Journal of Biological Chemistry with his name by Dr. Angelides in April 1989 at Ang. Ex. 118). The Panel, therefore, did not find credible Dr. Angelides's claim that he recalled "sending every

single manuscript that Dr. Elmer was associated with, like I have done for every student in my laboratory, whether they're in the laboratory or whether they've departed. For them to view the manuscript, to review it, to criticize it, and for them to send back constructive comments." Tr. at 1462.[90]

Second, the Panel was impressed by the credibility of Dr. Elmer's testimony in regard to the Brain Research paper. It was clear that Dr. Elmer was very reluctant to conclude that any errors in the paper could have been the result of Dr. Angelides's intentional action. He had a long-standing and close personal relationship with Dr. Angelides, supported him before the Baylor Sub-Committee, and willingly assumed responsibility for his own failure to maintain more organized records. See, e.g., Tr. at 923-25, 942, 1007-09, 2050. Dr. Angelides suggested that Dr. Elmer's conclusion that the misstatements at issue here were in fact intentional falsifications and not the result of honest error undermined Dr. Elmer's credibility and reflected undue influence on him by Baylor or ORI. However, comparison of Dr. Elmer's testimony before us on the points discussed above with the portions of his testimony before the Baylor Sub-Committee that are in the record reveals that his factual account of events is not significantly different. To the extent that his interpretation of the events has changed, he explained the change as the result of his having been provided with the opportunity to fully review his own data records. He described the result of this review as an "epiphany" in which he recognized that the misrepresentations of which he had become aware were too numerous and significant to have been the result of honest error. Tr. at 987-90, 1012. As to the data presented in the Brain Research paper, Dr. Elmer concluded that "it's very clear that the primary data that was represented as if it were something else, was not what was represented." Tr. at 2046. The Panel found this conclusion well-supported and corroborated by the evidence before it.

D. Grant Application Claims about Sodium Channel Antibodies

In addition to the presentation in publications of the results of sodium channel antibody project, Dr. Angelides also included data from this project in three grant applications that are alleged to include falsified material. ORI Findings ## 4F, 4G, and 4H, at 57, 58, 60, and 62. On September 12, 1988, Dr. Angelides forwarded to NIH a supplemental submission for grant application NS26672-01, the consideration of which had been deferred on July 29, 1988. Record Ex. 7. Grant application NS24606-05 was signed by Dr. Angelides on June 28, 1989. Record Ex. 9. Grant application NS28072-01A1 was signed by Dr. Angelides on October 26, 1989. Record Ex. 8. According to the Baylor Sub-Committee, only grant application NS28072-01A1 was funded. Baylor Report at Table II.B.2.

[90]Some students and collaborators reported that they did participate fully in the drafting process of papers that they published with Dr. Angelides. See, e.g., Hicks WD at 5; Joe WD at 5. However, the conclusion the Panel reaches here is not that Dr. Angelides never properly sought input from co-authors in the drafting process but rather that he did not always do so.

Two of these grant application submissions contained figures that presented data identical to those found to have been falsified in relation to Figures 2A or 3 of the Brain Research paper and made the same claims about the identification of those data that we have found above to be false. In each of those grants, however, two lanes of data were added to those presented in Figure 3 of the Brain Research paper. In a third grant application, one lane of data is included in a figure as showing 7493 recognizing a 260 kDa species, consistent with the presentation of those same data in Figure 3 of the Brain Research paper, whereas that lane is identified in the primary data and in Dr. Elmer's thesis as showing a lower molecular weight band. Although many of the arguments in relation to the data in these grant applications were the same as those already addressed in relation to the Brain Research paper figures, we discuss them separately here in order to consider whether Dr. Angelides has been shown to have been the party responsible for the misstatements in each application and whether the misstatements in each application have been shown to be intentional.

Dr. Angelides did not dispute that the same data were presented in the challenged figures in these grant applications (as detailed below) as in the Brain Research paper figures, but contended that the grant application figures were not falsified for the same reasons he advanced to contest the allegations in regard to the Brain Research paper. Ang. Br. at 240-41. He contended that mistakes were propagated from earlier manuscripts of what became the Brain Research paper into the grant applications. Ang R. Br. at 223; Tr. at 1376-81. Dr. Angelides contended that Dr. Elmer provided the data for these figures. Ang. R. Br. at 224-25. In addition, Dr. Angelides argued that ORI failed to prove that the specific figures contributed to a favorable review of NS28072-01A1. Ang. Br. at 241.

1. Primary data in grant application figures on sodium channel antibodies

a. <u>NS28072-01A1 appendix</u>:

Figure 1B presents the same Western blot data as appears in Figure 2A of the Brain Research paper. **Figure 1C** presents as lanes 1-4 the same Western blot data as appear at lanes 1-4 of Figure 3 in the Brain Research paper and presents as lanes 10-13 the same Western blot data as appear in lanes 9-12 of Figure 3 in the Brain Research paper. In each case, the data are identified in the figure legends in NS28072-01A1 in substantially the same way they were in the Brain Research paper.[91] However, Figure 1C of NS28072-01A1 contains two additional lanes of data

[91]The ORI Findings contain one apparent error in detailing the misstatements in the grant applications in relation to these three lanes. ORI charged that the source of the antigen in lane 10 of Figure IC in the NS28072-01A1 grant and Figure 4C in the NS24606-05 grant was falsified. ORI Findings at ## 4-F, at 57-58, and 4-G, at 60. However, lane 10 of those figures corresponds to lane 9 of Figure 3 of the Brain Research paper, identified in all three legends as rat brain, and no charges were made that the antigen in that lane was anything other than rat brain. We therefore find no evidence that the antigen source of lane 10 in the grant application figures was

(continued...)

that do not appear in Figure 3. Lane 5 showed 7493 tested against rat spinal cord; lane 14 showed 7493 tested in Schwann cells. The primary data for lane 5 appear as lane 2 in the same array of primary data from which the other lanes used here and in Figure 3 of the Brain Research paper were drawn and the tissue source identified in the grant is consistent with the label on the primary data. However, a relatively light band in that lane is shown in the primary data as approximately 180 kDa, whereas the grant asserts that the antibody is shown as recognizing a 260 kDa protein in that lane. Record Ex. 8, at 23. Neither party identified primary data for lane 14, but Dr. Angelides asserted that this lane represented data referenced in early drafts that Dr. Elmer reviewed for what became the Brain Research paper and was part of the planned 18-lane figure. Ang. R. Br. at 223-24; Record Ex. 44, at Att. III.20; Ang. Ex. 10.

b. NS24606-05 appendix:

Figure 4B presents the same Western blot data as appear in Figure 2A of the Brain Research paper (hence, also the same as that in Figure 1B of NS28072-01A1). **Figure 4C** presents the same data as appear in Figure 1C of NS28072-01A1, including lanes 5 and 14 which did not appear in Figure 3 of the Brain Research paper.

c. NS26672-01 Deferral:

Figure 2E presents data in lane 6 purporting to show that 7493 "recognizes only a 260 kDa" protein in rat brain once prepared with proper protease inhibitors. The primary data shown as lane 6 in Figure 2E also appear in Figure 3 of the Brain Research paper as lane 1, where they are also identified as 7493 reacting with a 260 kDa species in rat brain. The same lane of data appeared in Dr. Elmer's thesis in Figure 5-3, lane 3, where the molecular weight of the band was described as 180 kDa, consistent with the notation in the primary data.

2. Responsibility for preparation of grant application figures on sodium channel antibodies

Dr. Elmer testified that he did not prepare the data for these figures in the grant applications. Elmer WD at 6-9. He testified that he was never involved in writing the grant applications, that he did not prepare the final figures for them, and that he did not write the figure legends. Id. Instead he testified that Dr. Angelides would normally obtain raw data from him or directly from his (Dr. Elmer's) notebooks and would take it to Medical Illustrations himself to instruct them on how to create the final figure. Id. Dr. Elmer stated that he rarely reviewed any grant for accuracy before its submission and specifically testified that he was never shown any grant

[91](...continued)
misidentified.

application after his departure in June 1988. Id.[92] The Panel found Dr. Elmer's testimony in this regard credible and consistent with the general experience of other laboratory members discussed in earlier sections.

Dr. Elmer's testimony that he was not involved in the actual drafting of the grant applications is consistent with the testimony of many members of Dr. Angelides's laboratory to the effect that, while he might request data from others, Dr. Angelides drafted the applications himself without their review or participation. See, e.g. Benke WD at 3; Nutter WD at 7; Velazquez WD at 2; Wood WD at 4-5. Given the weight of the testimony that Dr. Angelides took sole responsibility for the grant application drafting process in general, it is even less likely that Dr. Elmer had any opportunity to review and correct the presentation of his data in these grant applications than was the case with the papers discussed previously.

The timing of the submission of the grant applications is also consistent with the testimony of Dr. Elmer that the presentation of his data in drafts of the Brain Research paper was accurate in the versions he worked on but diverged after he left the laboratory. Elmer WD at 47-48. These grant applications were all submitted after Dr. Elmer's departure. While one was submitted during the time Dr. Elmer was still visiting the laboratory to complete his thesis, no evidence was presented that he worked on any grant application during that period and Dr. Elmer expressly testified to the contrary. Elmer WD at 6. The Panel found it unlikely that Dr. Elmer approved presenting these data falsely in grant applications to fund a laboratory of which he would not be a part at the very time he was preparing a thesis presenting the same data accurately (and less favorably to himself) where its interpretation would most directly affect him.

Dr. Angelides suggested that the 14-lane figure used in the two grant applications came from either a handwritten draft manuscript by Dr. Elmer or an 18-lane figure in the manuscript version known as "Voltage.KJA," and, therefore, evidenced Dr. Elmer's involvement in preparing the figures that ended up in the grant applications. Ang. R. Br. at 223-24. As we noted above, Dr. Elmer testified that he never produced such a figure, and Dr. Angelides has not provided the figure or any evidence of its existence apart from his own testimony.

3. Intentionality of misrepresentation of data on sodium channel antibodies in grant

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[92]Dr. Angelides argued that Dr. Elmer previously stated in a letter that he had prepared composites of his data for grant applications. Ang. R. Br. at 224-25. Dr. Angelides did not produce the cited letter or enclosures for the record. However, even on the face of the language quoted by Dr. Angelides, Dr. Elmer said only that he did not remember specifically being asked to prepare data for a grant application, and that it was not likely "if the submission dates were 1/88 and 4/88." Id. This quotation, thus, does not relate to any of the grant applications discussed here, all of which were submitted after September 1988. Nothing in the quoted language contradicts Dr. Elmer's testimony before us that he did provide primary data for grants at times, but did not write or review the legends or texts presenting those data in the grants, and that he had no involvement in grant preparation after his departure from the laboratory.

application figures

Many of the reasons for which the Panel concluded that Dr. Angelides intentionally falsified his presentation of the same data in the Brain Research paper figures also apply to the figures in the grant applications, and we rely on them here as well. The data are generally clearly labeled on the array of primary data in a manner inconsistent with their presentation in the grant application figures. The same data are presented in Dr. Elmer's thesis in a manner consistent with the primary data. The misrepresentations consistently tended to make antibody 7493 appear more specific for the á subunit of the sodium channel in more kinds of tissues than would have been supported by an honest presentation of the primary data.

Further, the use of additional lanes and the presentation of the lanes in a different order in two of the grant application figures as opposed to Brain Research Figure 3 further demonstrate that errors were not merely propagated among manuscripts and grants. Rather, Dr. Angelides must have returned to the primary data in selecting data to present for various uses. This further supports the finding that the misrepresentations were intentional.

The Panel found that Dr. Angelides had a motive to misrepresent the data in these grant applications to support his claims about the specificity of the 7493 antibody, despite his claims that the falsifications were not material or not specifically required to respond to reviewers' comments. In the case of NS26672-01, Dr. Angelides in fact added the falsified data in direct response to reviewer comments. The NS26672-01 deferral submission responded to a letter from the study section secretary criticizing, among other things, the vague nature of the preliminary data and requesting clarification. Record Ex. 6. In his cover letter, Dr. Angelides specifically offered in response to that criticism that he had enclosed "further details and data on the characterization and properties of the sodium channel polyclonal and monoclonal antibodies," citing to Figure 2 which included the falsely-described lane. Cf. Record Ex. 7, at 3. In the case of NS28072-01A1, Dr. Angelides noted that he had revised the application in response to the study section critique and listed the changes he had made. Among the noted revisions are the addition of published papers relating to characterization of the monoclonal and polyclonal antibodies and an appendix offering further preliminary work and primary data on this project. Ex. 8, at 19. The Appendix includes the falsified data discussed in this section.[93] Thus, Dr. Angelides at least perceived that progress in the characterization of antibody 7493 was an accomplishment relevant to the reviewers of this grant. The aims of the application include the use of electron microscopy to study the distribution of sodium channel in axon membranes, for which antibodies that show affinity for mammalian sodium channel were needed and which had

[93]Notably, the revision of this grant in response to the critique also highlighted additional work in the preparation of anti-peptide antibodies supported by a presentation of primary data in another figure in the appendix which we conclude elsewhere was also intentionally falsified. The inclusion of false representations about multiple unrelated experimental results in support of a grant application being revised after criticism makes it more likely that the misrepresentations are intentional and not merely careless error.

been a "major goal" in which the laboratory had "invested considerable effort." Id. at 23. As Drs. Black and Waxman testified, the validity of electron microscopy results on sodium channel distribution and localization depends on the demonstration of the specificity of the antibody being used. Black WD at 10, 15; Waxman WD at 13, 21. The falsified data were directed at enhancing the appearance of specificity. Even in those instances where the data were not offered directly to respond to critiques, the presentation of antibody 7493 as more specific and as useful in more tissues than demonstrated by the primary data overstated the accomplishments and therefore the capabilities of Dr. Angelides's laboratory in a field that was, at the time, highly competitive and facing funding constraints. Hearing Ex. 7, at 4 (October 7, 1996 letter of Dr. Pfenninger). We conclude that the falsifications were material to the grants at issue and, therefore, were more likely to have been intentional.

In addition to his effort to attribute responsibility for the misstatements in these grant applications to Dr. Elmer, Dr. Angelides also argued that the Baylor officials who provided institutional certification of the applications were "equal signatories and are the parties responsible for the application." Ang. Resp. to ORI Charge Letter, Tab A at ¶451, at 56, ¶471, at 59, and ¶491, at 61. Dr. Angelides offered no basis to conclude that the institutional signatory was aware of or had any reason to suspect that data in the grant applications were presented falsely. The Panel found that Dr. Angelides's repeated deflection of responsibility to others further supported the conclusion that he acted intentionally in falsifying the data at issue.

4. Conclusion on grant application figures on sodium channel antibodies

For the reasons explained above, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides was responsible for the presentation of data in appendix Figures 1B and 1C of grant application NS28072-01A1, appendix Figures 4B and 4C of grant application NS24606-05, and appendix Figure 2E of the deferral submission of grant application NS26672-01. Further, the Panel concluded that the record demonstrates by a preponderance of the evidence that Dr. Angelides intentionally falsified each of these figures as follows:

- Figure 1B of NS28072-01A1 by misrepresenting the purity of antigen used in lanes 2-6;
- Figure 4B of NS24606-05 by misrepresenting the purity of antigen used in lanes 2-6;
- Figure 1C of NS28072-01A1 by misrepresenting the molecular weight of the reactive species in the first five lanes, and by misrepresenting the tissue source of the antigen used in lanes 4, and 11-13;

- Figure 4C of NS24606-05 by misrepresenting the molecular weight of the reactive species in the first five lanes, and by misrepresenting the tissue source of the antigen used in lanes 4, and 11-13; and

- Figure 2E of the deferral submission of grant application NS26672-01 by misrepresenting the molecular weight of the reactive species in lane 5.

The Panel concluded that Dr. Angelides's arguments in response to the evidence on this issue were not persuasive and that the conduct proven constituted scientific misconduct.

E. <u>Overall Conclusion Regarding the Anti-sodium Channel Antibodies</u>

Based on the evidence before it and for the reasons discussed in detail above, the Panel concluded that Dr. Angelides intentionally falsified data in five published papers and three grant applications relating to experimental results in the project of his laboratory to develop polyclonal and monoclonal antibodies to the mammalian sodium channel. In reaching this conclusion, the Panel considered each and every argument advanced by Dr. Angelides and reviewed all of the evidence presented by either party (whether or not specifically mentioned in the discussion) in separately evaluating each charge of falsification as to each individual instance in which the accuracy of the presentation of data was challenged. The Panel found evidence sufficient as to each of the instances of misidentification of data to conclude by a preponderance of the evidence that the data were falsified, that Dr. Angelides was the party responsible, and that he provided falsified data intentionally and not as a result of honest error or interpretation of data. Although the evidence as to each instance is thus sufficient in itself to find scientific misconduct, the Panel also concluded that the overall pattern of repeated misuse of the data further supported its findings in each instance that intentional falsification occurred. The Panel noted that, in each instance, the falsifications were material and self-serving in that they had the result of enhancing the perception of the accomplishments of Dr. Angelides's laboratory. The long period of time over which Dr. Angelides persisted in misrepresenting the results of the anti-sodium channel antibodies project (from September 1988 when the first challenged grant application was submitted to May 1990 when the PNAS paper was submitted) further reinforces the Panel's conclusion that Dr. Angelides acted intentionally. In many areas, Dr. Angelides's position was supported only by his own testimony and the Panel concluded that his testimony lacked credibility, given that it conflicted in so many respects with testimony of other, less interested, witnesses and with the documentary record.

Appropriate Remedies

Administrative debarment from grants and contracts is provided for by regulation. See 45 C.F.R. Part 76; 48 C.F.R. Subpart 9.4; and 48 C.F.R. Subpart 309.406. By means of an administrative debarment, individuals or entities are excluded from eligibility for grant and contract awards from the federal government for a specified period of time. Administrative debarments are discretionary actions taken to protect the interests of the public and the government and are not punitive. United States v. Glymph, 96 F.3d 722 (1996); 45 C.F.R. § 76.115 and 48 C.F.R. § 9.402(a) and (b). The regulations provide that the causes for debarment include:

> Any other cause of so serious or compelling a nature that it affects the present responsibility . . . .

45 C.F.R. § 76.305(d), 48 C.F.R. § 9.406-2(c).

Federal policy requires the award of grants and contracts only to responsible parties. Debarment is not mandatory upon a determination that a cause for debarment exists. A determination to debar is made after consideration of "the seriousness of the . . . acts or omissions and any mitigating factors." 45 C.F.R. § 76.300 and 48 C.F.R. § 9.406-1(a). In any debarment action, the cause for debarment must be established by a preponderance of the evidence, with the burden falling on the agency proposing debarment. 45 C.F.R. § 76.314(c)(1), (2); 48 C.F.R. § 9.406- 3(d)(3).

The standard for debarment does not mention scientific misconduct specifically as a cause for debarment. However, the "other cause" language of 45 C.F.R. § 76.305(d) and 48 C.F.R. § 9.406-2(c) would encompass scientific misconduct, where the misconduct is of so serious or compelling a nature that it affects the present responsibility of a person. Scientific misconduct of the types alleged in this case has been found to be an "other cause" justifying debarment in John C. Hiserodt, M.D., Ph. D., DAB No. 1466 (1994); Dr. David C. Bridges, DAB No. 1232 (1991); and in Robert Edward McCaa, Ph.D., DAB No. 823 (1987). See also Dr. Paul F. Langlois, DAB No. 1409 (1993).

Regulations governing debarment provide that the period of debarment shall be commensurate with the seriousness of the cause. 45 C.F.R. § 76.320(a), 48 C.F.R. § 9.406-4(a)(1). The regulations provide that generally, the debarment period should not exceed three years. However, a longer period of debarment will be justified in cases where circumstances warrant. 45 C.F.R. § 76.320(a)(1); 48 C.F.R. § 9.406-4(b).

In the present case, ORI contended that Dr. Angelides has engaged in a pattern of dishonest conduct that amounts to scientific misconduct as that term is defined in the DHHS regulations, 42 C.F.R. § 50.101, thereby exhibiting a lack of honesty and integrity that seriously and directly affects his present responsibility to participate in nonprocurement transactions of the federal government and to receive federal contracts. Based on the seriousness of the charges, ORI

therefore sought a recommendation from this Panel to the Debarring Official for debarment of five years. ORI also sought final approval of imposition for the same period of the following administrative actions:

1. Prohibition from serving in any advisory capacity to the PHS, including but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant;

2. Requirement that, subject to any debarment imposed, an awardee institution must monitor for accuracy any PHS sponsored research performed by Dr. Angelides[94];

3. Retraction, within 30 days of the date that this becomes a final action of the Department of Health and Human Services, of the falsified figures and text in each of the scientific papers in the journals PNAS, Glia, PRSL, ANYAS, and Brain Research, as a condition for eligibility of any future PHS grant awards.

ORI Charge Letter at 4-6.

The Departmental Appeals Board, through the RIAP, is authorized to hear appeals of findings of scientific misconduct. 57 Fed. Reg. 53,125 (1992); 59 Fed. Reg. 29,809 (1994). In cases where debarment is one of the proposed actions, the RIAP issues findings of fact and a recommended decision as to debarment. Regulations provide that, in cases of proposed debarment where additional proceedings (including an evidentiary hearing) are necessary, the Debarring Official may reject the findings of fact, in whole or in part, only after specifically determining them to be arbitrary and capricious or clearly erroneous. 45 C.F.R. § 76.314(b)(2), 48 C.F.R. § 9.406-3(d)(2)(ii).

As discussed above, the Panel concluded that all of ORI's charges against Dr. Angelides were supported by the preponderance of evidence in the record. For convenience, the charges upheld by the Panel are reproduced in an appendix to this decision.

Based on our findings of fact, the Panel concluded that the proposed debarment and administrative actions are warranted under the applicable laws because: (1) the conduct in which Dr. Angelides engaged over several years constituted a serious deviation from established norms in the scientific community that resulted in serious, damaging consequences for science

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[94]Under this action, any institution which submits an application for PHS support for a research project on which Dr. Angelides's participation is proposed, or which uses him in any capacity on PHS supported research, or which submits a report of PHS funded research in which he is involved would be required to concurrently submit -- (a) a plan for supervision of his duties, which must be designed to ensure the scientific integrity of his research contribution; and (b) a certification that the data provided by Dr. Angelides are based on actual experiments or are otherwise legitimately derived, and that the data, procedures, and methodology are accurately reported in the application or research report.

and other scientists; (2) Dr. Angelides's conduct showed a pattern of dishonesty that continued throughout the Baylor proceedings and the proceedings before this Panel; and (3) Dr. Angelides has demonstrated by his conduct a lack of present responsibility to receive and/or administer public research funds.

I. Dr. Angelides's conduct as established in this record constitutes serious misconduct resulting in serious consequences.

Most of the scientific misconduct established in the record consisted of Dr. Angelides taking primary data and reporting them falsely as the successful results of experiments that either had not been successful, or, in many cases, had not even been attempted. Forty figures in five journal articles and five grants were falsified; in some instances the same primary data were reused without changes, while in others the false identification was changed to a different false identification. While some falsifications merely enhanced the perception of, for example, the specificity of an antibody by reporting falsely the purity of antigen used, many misrepresentations, such as the claims respecting the project to insert unnatural amino acids into the sodium channel protein, were exaggerations of the accomplishments of Dr. Angelides's laboratory. All these falsifications tended to give Dr. Angelides an unfair advantage over honest scientists in competing for funds and for publication opportunities.

Dr. Angelides agreed that many items were false, but he frequently attempted to minimize their importance by claiming that the falsifications were not material to the grant application or journal article in which they appeared or were not required by or referred to by peer reviewers. As we note above in addressing these contentions, the co-authors of the journal articles did not agree with his assessment of the importance of the false data. Specifically, Drs. Black, Waxman and Elmer all agreed that it was an essential element of the four Yale papers that it be demonstrated that polyclonal antibody 7493 had been shown to react with the sodium channel in the tissues of interest in those papers. Black WD at 9-10; Waxman WD at 10-11; Elmer WD at 45, 51. Thus, the co-authors retracted these papers when the data reported for that element were called into question. In addition, many of the falsifications established in the record were specifically added to NS24606-05 Deferral in response to the reviewers' stated concerns about the feasibility of the projects proposed. This grant sought $2.1 million in funding. Record Ex. 9 at 1. A few falsifications, such as claims in two noncompetitive grants, did not have the gravity of identical claims in grant applications or resubmissions, but their divergence from other reports about the same experiments again demonstrated a conscious effort to deceive, rather than a repetition of prior errors, as part of an overall scheme to amplify the achievements of Dr. Angelides's laboratory.

Dr. Angelides's scientific misconduct and his subsequent behavior during the investigation of the charges against him adversely affected several scientists. When Dr. Angelides was confronted with proof that he had submitted grant applications containing falsified data, he blamed Dr. Wible and Mr. Lewallen for the falsifications and formally accused them of scientific misconduct. Although Baylor's investigation exonerated them, Dr. Angelides also named them

as codefendants in his civil lawsuit against Baylor, and they were obliged to hire lawyers to defend themselves. During the Baylor investigation and following issuance of the Sub-Committee's report, Dr. Angelides accused the Sub-Committee's members of either committing scientific misconduct in their handling of the investigation or being incapable of understanding the scientific issues involved. He also named all of them as codefendants in his civil law suit. Even scientists whose integrity was never questioned suffered. Drs. Black and Waxman felt themselves obliged to retract all the papers that included suspect data, Black WD at 20, and Dr. Waxman testified that much of the work of one of his graduate students with the antibody was wasted. Waxman WD at 33. In response to the question, "Has the situation had any effects on you?" Waxman testified:

> I have spent a lot of sleepless nights because of this situation. My colleagues and I trusted Dr. Angelides. We depended on his data in good faith. The situation is extremely disturbing. As scientists, I feel that all we have is truth and credibility. It is horrendous to think that data, included in a paper that I published, might have been falsified. I have asked myself, "Will anyone ever trust data in my papers again?" I have asked myself, "Short of looking over the shoulders of my collaborators as they do their experiments, can I ever trust a collaborator again?"

Id. In addition, Dr. Jones reported that his reputation was besmirched by his association with Dr. Angelides's laboratory. Tr. at 508-09.

For all the reasons summarized above, as well as the particular findings of scientific misconduct that we have found established by the preponderance of the evidence in this record, the Panel concluded that the conduct of Dr. Angelides in this matter has seriously deviated from standards accepted in the scientific community and has damaged science and scientists. Consequently, the Panel concluded that this misconduct is of so serious and compelling a nature that it affects the present responsibility of Dr. Angelides.

II. Dr. Angelides's conduct demonstrates a pattern of dishonesty for many years.

The testimony of students or researchers who worked in Dr. Angelides's laboratory over the years established that they had concerns about his willingness to misrepresent results and methods or overstate progress and achievements even before the present charges first came to light and cut across many areas of his work. See, e.g., Benke WD at 11; Woods WD at 7-10. The earliest instance of falsification established in this record occurred in February 1988, with the submission of grant application NS26672-01. Additional grants with falsifications followed and, in February 1989, the PRSL paper falsely reported experiments that had taken place during 1987. During 1989 the Glia paper was also published, and at the end of that year NS24606-05 Deferral was submitted. As detailed above, Dr. Angelides submitted other papers and grant applications containing false statements during 1990 and 1991 and in January 1992, after all the experimentalists whose data he was using had left his laboratory, he submitted the GM48816-01 grant. The Panel notes that for each grant application submitted, Dr. Angelides signed as

principal investigator attesting, under penalty of law, that he knew that willful provision of false information in the application was a federal criminal offense. While Dr. Angelides tried to downplay the false statements found in his submissions, arguing that no scientist's work could stand up to such scrutiny, their abundance demonstrates a proclivity for dishonesty. Additionally, the Panel notes as factors further demonstrating the pattern of dishonesty during those years that some of these falsifications consisted of reusing falsified data with new labels (e.g., Elmer's Olmsted procedure experiment) and that some falsified claims of success escalated over time (e.g., claims of actual insertion of unnatural amino acids into proteins).

During the Baylor investigation the pattern of dishonesty continued. When confronted by the Baylor Sub-Committee with instances where data were clearly misrepresented, rather than accept responsibility as the senior scientist for the data reported in his grant applications and publications, Dr. Angelides maintained that scientists who had worked for him had lied to him, giving him false data that they knew were to be included in these submissions. See Record Ex. 29, at 1 (Feb. 10, 1993) (Letter from Dr. Angelides to Dr. Rich); Record Ex. 34, at 1 (May 31, 1993)(Letter from Dr. Angelides to Dr. Berget). Dr. Angelides told Dr. Jones, after his appearance as a witness before the Baylor Sub-Committee in 1993, that Dr. Wible was out to get him (Jones) and that she was jealous of him. Tr. at 523. In December 1993, Dr. Angelides told Drs. Black and Waxman that the items he sought to correct in the proposed Corrigendum for the Brain Research paper were mere typographical errors and were not a part of the Baylor scientific misconduct investigation, but both statements were completely, objectively untrue. Waxman WD at 25-26, 28-29. In addition, Dr. Angelides told Dr. Elmer that he was purposely not identifying all the errors in the proposed Corrigendum because he was concerned that if too many errors were identified in the letter, the journal editor would not agree to publish the letter of correction. Elmer WD at 55-57.

The Panel also observed a pattern of dishonesty by Dr. Angelides during its proceedings, through his testimony and through his attempt to manipulate the process. For example, Dr. Angelides testified before the Panel that the pages of Dr. Wible's primary data that were found in his file for GM48816-01 were not placed there by him, even though he had testified before the Baylor Sub-Committee about the file's provenance and contents without any indication that he did not recognize them as his own. Compare Record Ex. 19, at 382-385, 429-33 (Transcript of Sept. 23, 1993 appearance at Baylor) and Record Ex. 23, at 125-133, 162-165 (Transcript of Nov. 2, 1993 joint appearance with Dr. Wible at Baylor) with Tr. at 1880 (Angelides). He neither acknowledged nor explained this change in position, nor did he cross-examine Dr. Wible or any of the Baylor Sub-Committee witnesses in connection with the assertion he subsequently made in his brief about Dr. Wible or the Sub-Committee having fabricated the folder's contents. Dr. Angelides sought and received the Panel's assistance in ensuring that the entire Baylor record was present in the hearing room, but chose to argue in his posthearing brief that documents supporting his claims, e.g., about antipeptide antibodies, were extant without ever introducing any such documents. He also waited until months after the hearing to raise his spoliation claims. Dr. Angelides also testified before the Panel that he did not accuse Dr. Wible or Mr. Lewallen of

scientific misconduct (Tr. at 1643, 1660) when the record showed that he did, by filing a formal letter with NIH. Record Ex. 46, Att. V3, at A-186.

Based on these factors, as well as the record supporting our findings of scientific misconduct, the Panel concluded that Dr. Angelides's conduct from February 1989 to the present shows a pattern of dishonesty. The Panel concluded that this pattern of dishonesty is of so serious and compelling a nature that it affects the present responsibility of Dr. Angelides and therefore meets the legal standards for debarment and administrative sanctions.

III. Dr. Angelides's conduct demonstrates a lack of present responsibility.

The purpose of the administrative and debarment remedies proposed by ORI is to protect the Federal government from having to deal with an individual who has proven to be untrustworthy. The Panel found that Dr. Angelides's conduct demonstrates a lack of present responsibility so grievous that the remedies proposed by ORI are warranted.

First, Dr. Angelides did not accept responsibility as a principal investigator and head of his laboratory for the grant applications and journal articles found to contain falsified data. Instead, he attempted to blame the scientists whose data were misused, even when many of them had left the laboratory before the submission of the false data. Moreover, he kept adding to his list of people to blame. In addition to Dr. Wible and Mr. Lewallen, whom he implicated during the Baylor investigation, he added in his testimony before the Panel Drs. Elmer and Nutter.

Second, although he claimed that his "cooperation with the Baylor Committee was exhaustive and diligent" (Br. at 145), Dr. Angelides ceased cooperating with the Baylor investigation well before it had reviewed all the allegations. Specifically, when the Baylor Sub-Committee asked him in a November 23, 1993 letter (Record Ex. 45, Att. III.67) to explain discrepancies it had found between primary data and data reported in grant applications and publications involving the sodium channel antibodies and the antipeptide antibodies, Dr. Angelides refused to respond. Record Ex. 45, Att. III.66. This is inconsistent with Dr. Angelides's responsibility as a scientist to cooperate in ensuring scientific integrity, particularly since by that time he had raised allegations of scientific misconduct against Dr. Wible and Mr. Lewallen, both of whom were alleged to have furnished some of the questioned data.

Third, although Dr. Angelides himself articulated the prevailing standards of the scientific community as requiring that a principal investigator personally review and accurately report data in his grant applications and publications, many of the defenses and arguments he raised during this proceeding disclose that he lacks understanding of the meaning and importance of these obligations. He insisted that it was up to the Baylor investigators and ORI to establish his dishonesty by proving that no supporting data existed, rather than recognizing that he had an obligation to make claims in grant applications and publications only where such claims are supported by primary data. This shows that Dr. Angelides does not understand his responsibility as a principal investigator or scientist reporting progress in the field. He contended that because

he believed that his laboratory was achieving the kind of results he was reporting, he was not at fault for using these particular data without confirming that his descriptions were accurate. This position similarly shows that Dr. Angelides does not understand his responsibility to report accurately the results of experiments actually performed. He repeatedly argued that the false data were not material to the grant applications in which they appeared because the data should be considered "optional" unless it could be shown that reviewers requested or relied upon the specific data. This contention also demonstrated a careless attitude toward the accurate reporting of data that is contrary to the standards of the scientific community. These positions indicate that Dr. Angelides is in need of the type of supervision and oversight recommended as an administrative remedy by ORI. In addition, they validate ORI's position that Dr. Angelides is not currently responsible enough to be a principal investigator.

The role of a principal investigator in directing federally funded research consists of more than merely thinking of creative ideas, as Dr. Angelides did. It also requires assembling and leading a team to do the research proposed. Dr. Angelides's conduct in reporting data and in blaming members of his team rather than taking responsibility for his own actions disqualifies him as a responsible manager of federal research funds and as a mentor for young scientists. This lack of integrity is so severe that a period of debarment greater than three years is warranted.

Based on these factors, and the factors discussed above, the Panel concluded that the preponderance of the evidence in the record supports the findings and conclusions set forth above. Based on those findings and conclusions, the Panel hereby imposes the administrative actions recommended by ORI and recommends to the Debarring Official that a debarment be imposed against Dr. Angelides for a period of five years.

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Donald F. Garrett
Panel Member

_____

Regis B. Kelly, Ph.D.
Panel Member

_____

M. Terry Johnson
Presiding Panel Member

Senior Staff Attorney assigned to case: Leslie A. Sussan

APPENDIX

The Research Integrity Adjudications Panel concluded that the preponderance of the evidence in the record supported the following charges made against Kimon J. Angelides, Ph.D., by the Office of Research Integrity in it's Charge Letter dated March 10, 1997:

A. NIH Grant Applications

1. You falsified the research results discussed in the text of the NIH grant application GM48816-01 at pages 14, 15, 22, and 29 and in Figures 2A, 2B, 5A, and 5B. The Appendix Table I also contains information falsified by you about the development of successful anti-peptide antibodies.

2. You falsified the research results in Figures 8C, 10, 11, 12 and in the text at pages 6, 13, 15, 16, 22, and 25 in the NS24606-05 Deferral submission . The Appendix Table I also contains information falsified by you about the development of successful anti-peptide antibodies.

3. You falsified the research results in the text at pages 22-23, 24, and 28 and in Appendix Figures 4B and 4C in NIH grant application NS24606-05. In addition, the Appendix Table I also contains information falsified by you about the development of successful anti-peptide antibodies.

4. You falsified the research results in the text at pages 23 and 24 and in Appendix Figures 1B, 1C, and 2 in NIH grant application NS28072-01A1. You also falsified information about the anti-peptide antibodies listed in Appendix Table II of NIH grant application NS28072-01A1.

5. You falsified the research results about the identification of the disulfide bridges in the sodium channel and the methodology in NIH grant applications: NS01218-02 (p. 8), NS01218-03 (p. 7), NS01218-04 (pp. 7, 8), and NS01218-05 (p. 7). You also falsified the research results about the use of engineered tRNAs to insert fluorescent amino acids into the NaCh and other proteins in NIH grant applications NS01218-04 (p. 8) and NS01218-05 (p. 7-8).

6. You falsified the research results in Figure 2E of NIH grant application NS26672-01 Deferral.

B. Scientific Papers

7. You falsified the research results in Figure 1 of the published scientific paper "Membrane-associated sodium channels and cytoplasmic precursors in glial cells," by Minturn, J.E., Sontheimer, H., Black, J.A., Angelides, K.J. Ransom, B.R., Ritchie, J.M., and Waxman, S.G., in Ann, N.Y. Acad. Sci. 633:255-271 (1991) ("ANYAS paper").

8. You falsified the research results in Figure 1 of the published scientific paper "Sodium channels in the cytoplasm of Schwann cells," by Ritchie, J.M, Black, J.A., Waxman, S.G. and Angelides, K.J., in Proc. Natl. Acad. Sci. (USA) 87:9290-9294 (1990) ("PNAS paper").

9. You falsified the research results in Figures 2A and 3 of the scientific paper "The voltage dependent sodium channel in mammalian CNS and PNS: antibody characterization and immunocytochemical localization," by Elmer, L.W., Black, J.A., Waxman, S.G. and Angelides, K.J., in Brain Res. 532:222-231 (1990) ("Brain Research paper").

10. You falsified the research results in Figure 1 of the scientific paper "Immuno-ultrastructural localization of sodium channels at nodes of Ranvier and perinodal astrocytes in rat optic nerve," by Black, J.A., Friedman, B., Waxman, S.G., Elmer, L.W., and Angelides, K.J., in Proc. R. Soc. London B 238:39-51 (1989) ("PRSL paper").

11. You falsified the research results in Figure 1 of the scientific paper "Sodium Channels in Astrocytes of Rat Optic Nerve In Situ: Immuno-Electron Microscopic Studies," by Black, J.A., Waxman, S.G., Friedman, B., Elmer, L.W., and Angelides, K.J., in Glia 2:353-369 (1989) ("Glia paper").