CONFIDENTIAL

Investigation into Allegations that Dr. Jan Paul Muizelaar violated the Faculty Code of Conduct

Date: April 22, 2013
# TABLE OF CONTENTS

## I. INTRODUCTION

## II. EXECUTIVE SUMMARY OF FINDINGS

## III. OVERVIEW OF FACT-FINDING INVESTIGATION

A. Scope of Investigation
   1. Documents Collected and Reviewed
   2. Witnesses Interviewed
   3. Expert Consultant

## IV. RELEVANT FEDERAL REGULATIONS

A. Definition of “Research” Under Federal Regulations
B. Definition of “Human Subject” Under Federal Regulations
C. Overview of IND Requirements Under Federal Regulations
   1. Definition of “Drug”
   2. Definition of “Clinical Investigation”

## V. RELEVANT ACADEMIC AND PERSONNEL POLICIES

A. The Faculty Code of Conduct
B. The UC Davis Policy and Procedure Manual
C. University of California Standards of Ethical Conduct

## VI. PROCEDURES FOR REVIEW AT UCD

A. Function and Role of the IRB
B. Other Review Mechanisms

## VII. CHRONOLOGY

## VIII. ADMINISTRATIVE FACT-FINDING

A. Interview of Dr. John Anderson
B. Interview of Dr. David Asmuth
C. Interview of Gina Guillame-Holleman
D. Interview of Dr. Alex Kon
E. Interview of Eric Mah
F. Interview of Dr. Fred Meyers
G. Interview of Dr. J. Paul Muizelaar
H. Interview of Dr. Robert O’Donnell
I. Interview of Dr. Claire Pomeroy
J. Interview of Teresa Porter
K. Interview of Dr. Rudolph Schrot
L. Interview of Dr. Allan Siefkin
M. Interview of Karen Smith, R.N.
N. Summary of Evidence Concerning Record of Invention
O. CMS Report
   1. Patient 1’s Consent Form, Exhibit 120
   2. Patient 2’s Consent Form, Exhibit 128
   3. Patient 3’s Consent Form, Exhibit 132

## IX. ANALYSIS

A. History Regarding 2008 Patient
B. Patient 1 ......................................................................................................................... 61
C. Patient 2 ......................................................................................................................... 65
D. Patient 3 ......................................................................................................................... 67
E. Response to Issues Raised by Dr. Muizelaar ................................................................. 70
  1. Research vs. Innovative Care ..................................................................................... 70
  2. Statement of Dr. Skip Nelson in 2008 ........................................................................ 72
X. CONCLUSION .................................................................................................................. 73
I. INTRODUCTION

This investigation concerns alleged Code of Conduct violations by Dr. Jan Paul Muizelaar, Professor and Chair of Neurological Surgery, and Dr. Rudolph Schrot, Associate Professor, Neurological Surgery regarding their use of an intentional surgical wound infection procedure in three patients with terminal brain cancer (glioblastoma) and allegations that the procedure lacked proper approval by The University of California, Davis (“UCD”) Institutional Review Board (“IRB”) in violation of University policies. The specific procedure in question involved placement of bacteria, *Enterobacter aerogenes* ("*E. aerogenes*")), into an open wound and bone flap in the brain of patients with glioblastoma to create a wound infection. The procedure was devised based on the belief by some neurosurgeons, including Dr. Muizelaar and Dr. Schrot, that a postoperative wound infection on glioblastoma patients prolongs survival.²

Glioblastoma is a devastating and common type of malignant brain tumor—it has a poor prognosis with a median survival of approximately 14 months, even with aggressive therapy.² Throughout the course of this investigation, Dr. Muizelaar and Dr. Schrot have maintained that they acted in the best interests of the individual patients and that they provided the procedure in an effort to prolong the patients’ lives. This particular report pertains to my analysis of the allegations regarding Dr. Muizelaar.

---

¹ P. DeBonis, *et al.*, “Postoperative Infection May Influence Survival in Patients with Glioblastoma: Simply a Myth?” *Neurosurgery* 69:864-69 (2011), Exhibit 146 (“It has long been stated, in various reports throughout the years, that having an infection within or near the resection cavity after removal of a brain tumor can actually stimulate the immune function of the patient and promote a longer survival. This contention has been based largely on anecdotal reports and has never been substantiated.”)

² *Id.* at 864.
II. EXECUTIVE SUMMARY OF FINDINGS

Dr. Muizelaar violated the Faculty Code of Conduct, APM 015, by engaging in conduct that constitutes a serious violation of University research policies. Dr. Muizelaar failed to obtain the appropriate review and approvals required by UCD PPM 240-50 and FDA regulations, discussed in greater detail below. Dr. Schrot also failed to adhere to the University of California’s Standards of Ethical Conduct.

III. OVERVIEW OF FACT-FINDING INVESTIGATION

A. Scope of Investigation

The investigation was conducted pursuant to the August 22, 2012 charge letter and the January 10, 2013 amended charge letter from Maureen Stanton, Vice Provost—Academic Affairs. The letter asked me to conduct the review with the assistance of Melissa Jones, Stoel Rives, LLP, the fact-finder in the investigation. As noted in the charge letters, allegations have been made that Dr. Muizelaar and Dr. Schrot engaged in behavior which, if found to be true, could constitute violations of the University of California Faculty Code of Conduct, Academic Personnel Manual (“APM”) 015. Specifically, it has been alleged that Dr. Muizelaar and Dr. Schrot “introduced infectious bacteria into the brains of glioblastoma patients without prior approval or authority.” Although the charge letter and amended charge letter cited APM 015.II.C (“Types of unacceptable conduct”) and Policy and Procedure Manual (“PPM”) 240-50 (“Research Involving Human Subjects”), the letters also noted that the investigation may result in determinations that additional or different University policies are applicable.

1. Documents Collected and Reviewed

Below is a summary of the materials collected and considered. The complete list of the documents that were collected and considered in this investigation, along with documents, are submitted with this report in the Appendix.

a. Correspondence from counsel for Dr. Muizelaar and Dr. Schrot concerning the investigation, Exhibit 178;

---

3 August 22, 2012 letter from Vice Provost Maureen Stanton to Lisa Ikemoto, Professor of Law at n.1, Exhibit 166 (“Through the course of conducting the investigation, the investigators may find additional and/or different applicable University policies”); January 10, 2013 letter from Vice Provost Maureen Stanton to Lisa Ikemoto, Professor of Law at n. 1, Exhibit 173 (“During the course of the investigation, facts may be determined that suggest violations of additional provisions of the Faculty Code of Conduct and/or University policy. You are directed to consider such violations and, if appropriate, include an analysis of the pertinent facts and policy in your report.”)
CONFIDENTIAL

b. October 17, 2011 letter to Patricia A. Holobaugh of the U.S. Food and Drug Administration from Harris A. Lewin, Ph.D, Vice Chancellor for Research and the 24 exhibits cited and attached to that letter, Exhibit 159.

c. October 4, 2012 letter (21 pages) from Dr. Muizelaar and Dr. Schrot, sent to Professor Ikemoto and Melissa Jones (“Oct. 4, 2012 Muizelaar and Schrot letter”), enclosing 47 exhibits, Exhibit 168.

d. Emails from the investigation file of Gina Guillaume-Holleman, Exhibit 145.

e. Two emails dated [redacted], 2011 and [redacted], 2011, provided by Dr. Allan Siefkin, Chief Medical Officer, Exhibits 144-145.

f. Record of Invention form, dated [redacted], 2011, submitted by Dr. Muizelaar and Dr. Schrot to the Technology Transfer Services, Office of Research, U.C. Davis, Exhibit 130.

g. [redacted], 2011 letter to Dr. Muizelaar and Dr. Schrot from John Shih, Business Development and Patent Prosecution and Management, Office of Research, U.C. Davis, regarding “Disclosure and Invention: ‘Probiotic Cancer Therapy for Bacterial Oncolyisis,’” Exhibit 137.

h. Emails provided by former IRB Co-Chair Dr. David Asmuth regarding the IRB investigation and related issues, Exhibits 148-149.

i. Report by the Department of Health and Human Services Centers for Medicare & Medicaid Services (patient names redacted), signed by Chief Medical Officer Dr. Siefkin on December 6, 2012 (“CMS Report”), Exhibit 169.


k. Correspondence from counsel for Dr. Muizelaar and Dr. Schrot sent on multiple dates regarding various subjects related to the investigation, Exhibits 168, 178.

2. Witnesses Interviewed

In conducting the investigation, we interviewed the following individuals on the dates set forth below.

<table>
<thead>
<tr>
<th>Interviewee</th>
<th>Date</th>
<th>Attendees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eric Mah</td>
<td>10/22/2012</td>
<td>In person: Melissa Jones, Marcia Canning</td>
</tr>
</tbody>
</table>
3. Expert Consultant

In addition to conducting fact interviews and reviewing documents, we engaged an independent expert consultant in this matter, Dr. Robert J. Levine, Professor of Medicine and Lecturer in Pharmacology at Yale University, and Chair of the Executive Committee, Interdisciplinary Center for Bioethics. Dr. Levine is an internationally recognized expert on bioethics, human subjects research and institutional review boards. He is the co-author of the Belmont Report, which is discussed below and is incorporated by reference into the UCD Policy and Procedure Manual, Chapter 240. We provided Dr. Levine, on a confidential basis, a copy of the Chronology from this report, the letter from Dr. Muizelaar and Dr. Schrot to Professor Ikemoto and Melissa Jones, and the exhibits that were attached to that letter. We had several substantive discussions with Dr. Levine regarding issues related to the investigation, including FDA regulations, human subjects research, the role of the IRB and the facts and allegations at issue here. We also sought and received input from Dr. Levine regarding the analysis and conclusions set forth in this report.
IV. RELEVANT FEDERAL REGULATIONS

In 1974, Congress enacted the National Research Act, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.\(^4\) The Commission identified basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. The report from the Commission, known as the “Belmont Report” identified those ethical principles and made various recommendations.\(^5\) Many of the recommendations from the Belmont Report and from other reports issued by the Commission were later incorporated into the Department of Health and Human Services regulations (Title 45, Part 46) and in the FDA’s regulations (Title 21, Part 50 of the Code of Federal Regulations (“CFR”) and Part 56 of the CFR). As noted above, University Policy 240 requires that research done under the auspices of UCD involving human subjects must comply with state and federal regulations, including those sections of the CFR.

The following sections of the federal regulations have been considered in the course of this investigation: 21 C.F.R. Part 50, Protection of Human Subjects; 21 C.F.R. Part 56, Institutional Review Boards; 21 C.F.R. Part 54, Financial Disclosure by Clinical Investigators; and 21 C.F.R. Part 312, Investigational New Drug Application. We have also considered the FDA Draft Guidance for Industry; Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without An IND (October 2010), which was provided to Dr. Schrot by the IRB Director in November 2010, Exhibit 118.

A. Definition of “Research” Under Federal Regulations

The regulations define “research” as: “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.” 45 C.F.R. § 46.102(d) (2009).

B. Definition of “Human Subject” Under Federal Regulations

The Department of Health and Human Services’ regulations define “human subject” as “a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2)


\(^5\) The Belmont Report identified three ethical principles: respect for persons, beneficence, and justice. The report was issued in 1978; it first appeared in the Federal Register in 1979.
Identifiable private information.” *Id.* at § 46.102(f). The FDA’s regulations define “human subject” as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.” 21 C.F.R. § 56.102(e).

C. Overview of IND Requirements Under Federal Regulations

An Investigational New Drug is a “new drug or biological drug that is used in a clinical investigation.” 21 C.F.R. § 312.3(b). An “IND” is an investigational new drug application, also referred to as a “Notice of Claimed Investigational Exemption for a New Drug.” *Id.* Under federal law, a drug may not be transported or distributed across state lines unless it has an approved marketing application. 6 The IND is the means through which the sponsor technically obtains this exemption from the FDA.

The FDA recognizes various types of INDs: (1) a Sponsor-Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population; (2) an Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21 C.F.R. sections 312.23 or 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist; and (3) a Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place. 7

---


7 As explained in the Department of Health and Human Services’ IRB Guidebook, available since 1993, the “FDA permits Treatment INDs only for drugs that show some promise of therapeutic benefit. Two standards exist: For serious diseases, applications for Treatment INDs must show sufficient evidence of safety and effectiveness to support the use. Ordinarily, this standard means that a drug may be made available for treatment use either during Phase 3 investigations or after all clinical trials have been completed. For immediately life-threatening diseases, the evidence, taken as a whole, must show (i.e., there must be sufficient data reasonably to conclude) that the drug may be effective for its intended use in its intended patient population and would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. Under this standard, investigational drugs for (continued . . .)
An IND is required under the federal regulations, part 312, where all of the following exist:

- The research involves a drug as defined under the federal regulations;
- The research is a clinical investigation as defined in the IND regulations (21 C.F.R. 312.3); and
- The clinical investigation is not otherwise exempt from the IND requirements in part 312.8

As stated in 21 CFR 312.2(b), clinical investigation of a drug is exempt from the IND regulations if the drug is lawfully marketed in the United States and all of the following are true:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
(v) The investigation is conducted in compliance with the requirements of 312.8 (Promotion and charging for investigational drugs).

As noted above, and confirmed by the expert consultant in this matter, clinical investigations that are exempt from IND regulations still require IRB review and approval.

(. . . continued)

FDA Draft Guidance for Industry; Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without An IND (October 2010), referred to herein as “FDA 2010 Draft Guidance,” Exhibit 118. As discussed below, IRB Director Eric Mah provided a link to this document to Dr. Schrot in November 2010, before the procedure was conducted on Patient 2.

8 FDA Draft Guidance for Industry; Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without An IND (October 2010), referred to herein as “FDA 2010 Draft Guidance,” Exhibit 118. As discussed below, IRB Director Eric Mah provided a link to this document to Dr. Schrot in November 2010, before the procedure was conducted on Patient 2.
1. Definition of “Drug”

The FDA defines “drug” as, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. . .” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” 21 U.S.C. § 321 (g)(1) (Federal Food, Drug & Cosmetic Act § 201(g)(1)). Biological products subject to licensure under section 351 of the Public Health Service Act (42 U.S.C. § 262) may also be considered drugs. In addition, the definition of drug is not limited to compounds intended for therapeutic purposes; it also includes compounds intended to affect the structure or function of the body, without regard to whether the compound is intended to influence a disease process.9 In addition, the FDA Draft Guidance confirmed that an IND is required for studies “in which a live organism (e.g., virus, bacteria, or fungi that is modified or wild-type) is administered to subjects to study the pathogenesis of disease or the host response to the organism (see part 312)” and that the organism is a biological product “and a drug.”10

2. Definition of “Clinical Investigation”

Under 21 C.F.R. 312(b): “Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.” (Emphasis in original.) As explained in the FDA 2010 Draft Guidance, “the number of subjects enrolled has no bearing on whether the study is subject to the IND regulations. The definition of clinical investigation specifically includes studies with as little as one subject.” (Emphasis in original.)11

Furthermore, as clarified by the FDA Draft Guidance, the belief that IND regulations “do not apply to clinical investigations that are not intended to investigate a drug’s potential for commercial sale” is incorrect. “Whether the IND regulations apply to a planned clinical investigation does not depend on whether the intent of the clinical investigation is commercial or noncommercial.”12

---

9 See summary of regulations set forth in the FDA 2010 Draft Guidance, Exhibit 118.


V. RELEVANT ACADEMIC AND PERSONNEL POLICIES

We reviewed and considered several University policies that may be applicable to the allegations made against Dr. Muizelaar and Dr. Schrot.

A. The Faculty Code of Conduct

The Faculty Code of Conduct, Academic Personnel Manual 015 (“APM”), contains information regarding “Types of Unacceptable Faculty Conduct.” The APM Preamble provides “examples of types of unacceptable faculty behavior which are subject to University discipline because, as stated in the introductory section to Part II, they are ‘not justified by the Ethical Principles’ and they ‘significantly impair the University’s central functions as set forth in the Preamble.’” See APM 015 at p. 2.

Section II.C., under subsection “The University,” of APM 015 states:

Types of unacceptable conduct:

7. **Serious violation** of University policies governing the professional conduct of faculty, including but not limited to policies applying to research, outside professional activities, conflicts of commitment, clinical practices, violence in the workplace, and whistleblower protections.”

(Emphasis added.)

B. The UC Davis Policy and Procedure Manual

The UCD Policy and Procedure Manual (“PPM”) Chapter 240, Research Involving Human Subjects, Section 50, Principles and Policies provides, in pertinent part:

All research done under the auspices of UCD in which human subjects are involved must be reviewed and approved by the Human Subjects Review Committee (HSRC) appointed by the

---

13 Section 50 of the UCD PPM was enacted in March 1987 and thus, was in place well before the events at issue here.

14 As further explained in Chapter 240, Section 50 of the UCD PPM, the HSRC “functions as the UCD’s institutional review board (IRB). The Committee is charged with review and approval of research involving human subjects, unless such activities are specifically exempted from review by the Committee (refer to Section 240-54 and 240-55).” UCD PPM Chapter 240, Section 50, Principles and Policies, at V.C. The exemptions discussed in Section 240-54 and 240-55 are not applicable here.
Chancellor according to the requirements set forth in Title 45, Part 46 and Title 21, Part 56 of the Code of Federal Regulations. Review and approval of use of human subjects in research according to Federal, State, and University policy applies to all studies in all locations, whether funded or unfunded, and whether conducted by faculty, students, or staff...No such study may begin before it has been so approved, nor may it continue past its approved term.

In addition, UCD PPM Chapter 240 explicitly references the Belmont Report, noting: “The University of California, Davis, subscribes to the concepts set forth in the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Exhibit A) and accepts as basic principles the following [in pertinent part]:

D. Prior animal research

Whenever possible and relevant, animal research will precede research on human subjects.

UCD PPM Chapter 240 states that “Human subject of a clinical investigation—(FDA) For purposes of FDA regulations, means an individual who is or becomes a participant in research either as a recipient of a test article or as a control.” It notes that a human subject may be “[a] patient to whom the test article might offer a therapeutic benefit or provide diagnostic information or a better understanding of a disease or metabolic process....”

Notably, the UCD PPM, Chapter 240, in its definition of research, notes that “[t]he use of an investigational drug or device automatically identifies an activity as research.” It likewise states that a “surgical procedure is considered to involve research” if “[t]he investigator wishes to develop a procedure that has not previously been performed,” or if “[t]he investigator wishes to study a procedure that is not accepted therapy or that might not be considered ‘best medical care.’”

---

15 The Vice Chancellor-Research, acting as the Institutional Officer, actually appoints the members of the IRB, as delegated by the Human Research Protection Program Plan.

16 Id. at I.D.

17 Id. at V.B, V.B.2.

18 Id. at V.G.1 (emphasis added).

19 Id. at V.H., V.H.2-4.
The term “investigator” is defined in the UCD PPM as “a person who is responsible for and conducts research. Responsible investigators at UC include its faculty, students, staff, and administrators.” It also notes that under FDA regulations, an investigator is “an individual who actually conducts a clinical investigation, or in the event of an investigation conducted by a team of individuals, is the responsible leader of that team [21 C.F.R. 56.102(h)].”

The UCD PPM, Chapter 290, Health and Safety Services, Section 55, Biological Safety, identifies the activities that require approval of a Biological Use Authorization (“BUA”) by the Biological Safety Administrative Advisory Committee (“BSAAC”). Such conduct requiring approval of a BUA by the BSAAC includes:

3. Research and other activities involving the use of microbial agents listed as Risk Group 2 or 3 (see NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL, fifth edition or later), the NIH Guidelines, or the UC Davis Biosafety Manual), or agents that are customarily handled at Biosafety Level 2 or 3 regardless of Risk Group.

*Enterobacter aerogenes* falls under Biosafety Level 2, according to the UCD Biosafety Manual, Appendix A.

C. University of California Standards of Ethical Conduct

The Standards of Ethical Conduct, adopted by the Regents of the University of California in May 2005, states in the “Ethical Conduct of Research” section:

All members of the University community engaged in research are expected to conduct their research with integrity and intellectual honesty at all times and with appropriate regard for human and animal subjects. **To protect the rights of human subjects, all research involving human subjects is to be reviewed by institutional review boards.**

The Standards of Ethical Conduct also has a section on “Conflicts of Interest or Commitment,” which provides in pertinent part that “In all matters, community members are...”

---

20 Id. at V.D.

21 Id.

22 University of California, Standards of Ethical Conduct, Ethical Code of Conduct in Research, available at www.ucop.edu/ethics-compliance-audit-services/compliance/standards-of-ethical-conduct.html. (Emphasis added.)
expected to take appropriate steps, including consultation if issues are unclear, to avoid both conflicts of interest and the appearance of such conflicts.”

VI. PROCEDURES FOR REVIEW AT UCD

A. Function and Role of the IRB

The function and role of the IRB “is to ensure adherence to all federal, state, local, and institutional regulations concerning the protection of human subjects in research. The UCD IRB review is required for both funded and non-funded human subjects research.” At UCD, there are four campus wide IRBs that exist to “safeguard the rights and welfare of all human research subjects and have the authority to approve, require modifications in, or disapprove all research activities that fall within their jurisdiction…UCD assures the government and the public that it will comply with federal regulations for the protection of human research subjects.”

B. Other Review Mechanisms

In March 2012, the medical staff developed an Innovative Care policy to provide guidance and oversight in the innovative use of medical therapies, devices and/or medications in the treatment of patients. Through the policy, the Innovative Care Review Committee considers information during the approval process to ensure that unapproved drugs, devices and biologics are used safely and in compliance with UCD policies and state and federal regulations.

Although the written Innovative Care policy was not in place during the time period in question here, there were several other approval mechanisms in place at UCD. In addition to the IRB, discussed above, during the relevant time period, the UC Davis Medical Center Bioethics Consultation Committee, medical staff peer review and review of the Chief Medical Officer were well-established review and approval mechanisms in place at UCD.

23 *Id.*

24 *See* http://research.ucdavis.edu/c/cs/hrp.

25 *Id.*

26 For instance, the Bioethics program was put in place at UCD Health System in 1996. *See* http://www.ucdmc.ucdavis.edu/bioethics/; see also http://www.ucdmc.ucdavis.edu/ctsc/area/bioethics/Bioethics_Landing.html.
VII. CHRONOLOGY

27/2008: Dr. Muizelaar and Dr. Schrot begin discussions regarding the use of bacteria (*Enterobacter aerogenes*) to create an intentional wound infection in the brain of a patient who had been diagnosed with glioblastoma. At the time that this procedure is discussed, the patient had already received surgery, chemotherapy, and radiation therapy and had a recurrence of tumor.

28/2008: A meeting of the Bioethics Consultation Committee is held to consider the proposed intentional wound procedure on the patient. Dr. Schrot presents the case at the meeting and the committee members engage in a lengthy discussion. The committee determines that the procedure “may be seen as consistent with the customs and practices of medicine.” The committee believes, however that the procedure requires more oversight than it can provide and concludes in its report that: “The committee strongly felt that before moving forward this protocol should be reviewed by the institutional review board and approved as an experimental protocol.”

29/2008: Dr. Schrot emails Dr. Robert “Skip” Nelson, Pediatric Ethicist at FDA, describing the patient noting, “We are proposing an experimental protocol for a single patient.” Dr. Schrot asks for “some insight as to how to proceed with the IRB application” and notes that “[w]e have already had an ad hoc ethics committee meeting at UC Davis Medical Center, which has given us the thumbs up, pending IRB approval.”

---

27 This chronology summarizes events relevant to this investigation, in chronological order. Although only excerpts of documents are quoted herein, the documents are provided in full in the Appendix to this report.


29 Kon Interview, February 4, 2013.

30 Then Chair of the Bioethics Consultation Committee at UCD, Alex Kon, has explained that the Bioethics Committee did not intend any specific meaning to be given to the term “experimental” as it was used in the report or assign any significance to the use of that term. The Bioethics Consultation Committee simply felt that more oversight was needed for this proposed procedure than the Committee could provide and thus, recommended referral to the IRB.

31 Email from Dr. Schrot to Dr. Nelson, dated 2008, Exhibit 104.
CONFIDENTIAL

2008: Dr. Nelson replies to Dr. Schrot, noting that if the product “is only available under IND, you would need to work through CBER” and copies Sara Goldkind of the FDA to assist Dr. Schrot in negotiating the FDA process.32

2008: Dr. Schrot emails a copy of the clinical protocol for the intracranial bacterial therapy to Dr. Stephanie Simek at FDA, copying a number of recipients including Dr. Muizelaar and members of the IRB (Dr. Asmuth and Dr. Anderson).33

2008: Dr. Asmuth informs Dr. Schrot that “you will need to fill out a full committee application,” referring to the IRB committee, and puts him in touch with IRB staff for assistance.34

2008: Dr. Schrot submits IRB Full Committee Review Application Form.35 He writes in the Conclusion of the application: “Further pre-clinical work is needed before a larger scale trial is implanted [sic], but we feel that the current observational and existing pre-clinical evidence supports a single therapeutic trial of probiotic intracranial therapy in an otherwise dismal prognosis for the patient in question…We feel, therefore, that therapeutic innoculation [sic] of the tumor cavity with a known strain of Enterobacter aerogenes with antibiotic rescue offers a reasonable risk/benefit ratio in this patient.”

2008: Dr. Anderson emails Elodia “Lody” Tarango, Dr. Asmuth, and Dr. Schrot and notes that given the urgency, he would be “inclined to have it go forward even without full committee final approval (assuming the FDA doesn’t have expressed problems with this). It would still be appropriate for it to go to full committee for the purpose of additional potential patients.”36

2008: Dr. Schrot discusses procedure with Center for Biologics Evaluation and Research. Dr. Riggins, FDA, emails Dr. Schrot to confirm the discussion he and Dr. Przepiorka had with Dr. Schrot on 2008. His email contains a list of 11 comments and states that “animal studies will be necessary prior to entering into the clinic with your proposed therapy.”37 It further states: “Additionally, Dr.

32 Id.

33 Email from Dr. Schrot to Dr. Simek, dated 2008, Exhibit 106.

34 Id.


36 Email from Dr. Anderson to Elodia Tarango, dated 2008, Exhibit 108.

37 Email from Patrick Riggins to Dr. Schrot and others, dated , 2008, Exhibit 111.
Przepiorka further pointed out that these animal studies must show not only safety, but also establish a reasonable proof of concept in order for this investigational therapy to be introduced into patients.”

2008: Dr. Schrot emails Dr. Anderson to advise him that he just spoke with FDA and “there are very stringent criteria for any biologic to be tested in a human, which includes about 9 criteria which need to be satisfied in an animal model…FDA cannot approve this trial in a human.”

2008: Dr. Anderson responds to Dr. Schrot’s 2008 email noting “I would interpret this to mean that the FDA (and us) won’t allow this product to be used in humans without further testing,” and making related suggestions.

2008: Dr. Schrot emails Dr. Kon, Dr. Anderson, Dr. Asmuth and others to note that the proposed protocol has been suspended “since the FDA, and hence the IRB, cannot currently approve the protocol without further pre-clinical studies to support the use of an IND…”

2008: Dr. Kon responds to Dr. Schrot and suggests that it might be reasonable to ask the IRB to request a 50.54 panel review with the IRB if he desires to move forward.

2008: Dr. Lorena Navarro orders bacteria from ATCC, requiring a Material Transfer Agreement (MTA). The MTA defines “Biological Materials” as “ATCC Materials, Progeny, Unmodified Derivatives and Modifications, either individually or jointly.” The MTA defines “Progeny” as “an unmodified descendant from the ATCC Materials, such as virus from virus, cell from cell, or organism from organism.” The Scope of Use in the MTA provides in part: “The Biological Materials are not intended for use in humans.” Neither Dr. Schrot nor Dr. Muizelaar are signatories on the MTA.

38 Email from Dr. Schrot to Dr. Anderson, dated 2008, Exhibit 109.

39 Id.

40 Email from Dr. Schrot to Dr. Kon and others, dated 2008, Exhibit 111.

41 Id.

42 ATCC “is an independent, private, nonprofit biological resource center (BRC) and research organization.” See www.atcc.org/About/tabid/138/Default.aspx

43 Material Transfer Agreement and purchase order, exhibit 7 to Lewin letter to FDA, Exhibit 159.
2008: Dr. Schrot is listed as the primary investigator on a rat study under the oversight of the UCD’s Institutional Animal Care & Use Committee (“IACUC”) and Dr. Muizelaar arranges for internal funding of a graduate student to assist in that study.\footnote{IACUC Protocol [Ex. 5 to FDA letter], Exhibit 159.} The Protocol for the rat study states in part: “The object of this study is to demonstrate a therapeutic effect of intracranial infection with a gram-negative organism on a rat model of glioblastoma. These experiments will demonstrate a proof of principle that live bacteria can fight brain cancer.” Under the “Significance” heading, the Protocol notes: “Promising results in our pre-clinical investigations could open the door to FDA approved phase I clinical trials in humans, offering new hope to patients whose lives are otherwise cut short by this deadly tumor.”

2008: Dr. Schrot submits a Biological Use Authorization Application/Recombinant DNA Project Registration, listing Dr. Navarro as a co-investigator.\footnote{Biological Use Authorization, exhibit 6 to Lewin letter to FDA, Exhibit 159.} The Application notes that the infectious agent that will be used is \textit{Enterobacter aerogenes} to be obtained from the ATCC.

2008: Dr. Schrot prepares and submits a Grants Application Package for “Probiotic Therapy for Malignant Glioma.”\footnote{Grants Application Package submitted by Dr. Schrot, Exhibit 113.} The Project Summary in the application describes the background for the project, noting: “This research tests the proof of concept that intracranial bacterial infection provides a therapeutic benefit in glioblastoma, providing a pre-clinical framework for human trials.” The Grant Application includes a letter of support from Dr. Muizelaar, among others.

2009: Eric Mah begins working as UCD IRB Director.

2009: Dr. Lorena Navarro emails Dr. Schrot to update him on the status of the orders for bacteria, noting that she received bacteria the day before but that she is still waiting for the syringes and needles to arrive. She notes that she is “beginning to culture” it.

2009: Research begins on the use of bacterial infection to treat brain tumors in rats in Dr. Navarro’s laboratory. Graduate student\[
\text{[Redacted]}\] assists.

2009: NIH issues Summary Statement to Dr. Schrot regarding his grant application for his project: “Clinical Neuroimmunology and Brain Tumors Study Section.”
NIH comments in the Summary Statement notes numerous weaknesses with the proposal, including that the proposal has “[l]ow translational impact with seriously flawed methodology and statistical analysis.” The NIH Summary Statement also comments: “This is a very poorly developed scientific proposal that lacks feasibility” and that “There is absolutely no feasibility evidence in support of the project.” It also comments that the proposal has a “[l]ow translational impact since it is very unlikely any IRB or the FDA will allow the introduction of Enterobacter aerogenes directly into patients.”

2010: Dr. Muizelaar is contacted by [redacted], referred to herein as Patient 1, who had been diagnosed with glioblastoma earlier and had received treatment at [redacted]. Prior treatment efforts, including surgery and medication, had failed and [redacted] family approached Dr. Muizelaar to discuss the options for the intentional wound infection procedure.

2010: Dr. Muizelaar speaks with CMO Dr. Siefkin after an office visit with Patient 1. Dr. Siefkin recalls that during the conversation, Dr. Muizelaar stated that the IRB had told Dr. Schrot the procedure would not be considered research. Dr. Siefkin makes recommendations regarding informed consent.

2010: Dr. Schrot contacts Mr. Mah by telephone regarding the proposed procedure on Patient 1. Dr. Schrot informs Mr. Mah that bacteria that will be used in the procedure is local and that the patient has a rare disease.

2010: Mr. Mah sends follow-up email to Dr. Schrot noting in part: “Based on our conversation, I do not believe this requires IRB review as it does not qualify as human subjects research. Furthermore, the procedure does not appear to fall under the auspices of the FDA’s authority because you are treating a single patient in the course of clinical care and not as part of research and are not trying to obtain the drug/biologic from on outside source.” His email also notes: “I

47 NIH Summary Statement at 2, Exhibit 117.
48 NIH Summary Statement at 4, Exhibit 117.
49 NIH Summary Statement at 3, Exhibit 117.
50 Siefkin interview, November 13, 2012.
51 Mah Interview, October 22, 2012.
52 Email from Mah to Dr. Schrot, dated [redacted], 2010, Exhibit 119.
CONFIDENTIAL

have consulted with Chief Compliance Officer Teresa Porter and she recommends you seek guidance/approval from Chief Medical Officer Al Siefkin.”

2010: Dr. Muizelaar discusses the proposed procedure with Dr. Siefkin. Dr. Siefkin emphasizes the needs for extensive informed consent of both the patient and the family.\textsuperscript{53}

2010: Dr. Schrot prepares a special consent form for Patient 1 which advises that there is no proof that the proposed procedure might be beneficial, nor are there animal data to support it. It further notes that the procedure with live bacteria has never been tried before, the surgeons have no experience with it, and that the infection may be totally ineffective in treatment of the tumor. Patient 1 and review and sign the consent form.\textsuperscript{54}

2010: Dr. Muizelaar performs the procedure on Patient 1. Dr. Schrot is listed as a surgeon for the procedure on the UC Davis Health System file but has informed the fact-finder for this investigation that he did not perform or assist with the surgery.

2010: CMO Dr. Siefkin sends a lengthy and detailed email to Dr. Muizelaar, copying Dr. Schrot on the morning of regarding the proposed procedure. The email notes, inter alia, that since his conversation with Dr. Muizelaar, Dr. Siefkin has thought of three other items that need addressing: (1) complication from the procedure; (2) ethics; and (3) costs. His email notes: “I hope you will not view these additional thoughts as putting up road blocks in your attempt to help this patient. However since you have raised this issue with me (and it appears to have been pointed to me from Human Subjects) I feel obligated to ask that you now address these other issues also.”\textsuperscript{55} Dr. Muizelaar has informed the fact-finder for this investigation that he did not see this email before he started the procedure on Patient 1, but that he believes he had addressed these issues before the surgery.

2010: Patient 2, \textsuperscript{56}, has an office visit with Dr. Muizelaar. His notes on visit indicate that was diagnosed with a glioblastoma 2010, had

\textsuperscript{53} Letter from Dr. Muizelaar’s and Dr. Schrot’s counsel to Professor Ikemoto and Melissa Jones, at p. 7, Exhibit 168.

\textsuperscript{54} Consent form signed and dated, 2010, Exhibit 120.

\textsuperscript{55} Email from Dr. Siefkin to Dr. Muizelaar and Dr. Schrot, dated, 2010 (9:26 AM), Exhibit 121.
surgery and did well after surgery, but the recent MRI scan shows a recurrence of a large tumor and another probable tumor.\footnote{Office Visit notes for Patient 2, dated \textit{[blank]}, 2010, Exhibit 123.}

\textbf{2010:} Dr. Schrot contacts Mr. Mah about Patient 2, advising Mr. Mah that he believes might benefit from the bacterial infection procedure. Dr. Schrot indicates he has reviewed FDA guidelines and does not believe an IND is necessary for the procedure they propose.

\textbf{2010:} Mr. Mah emails Dr. Schrot, copying Dr. Muizelaar regarding the proposed procedure with Patient 2. He notes that “When we initially spoke, I understood the innovative/unconventional procedure was an extremely rare event with a terminally ill patient who was rapidly declining. Previously, as a single patient experience, the procedure would not qualify as human research under federal definitions. In addition, you described the use of bacteria as a form of procedure in the course of your practice of medicine (not a clinical investigation or experiment). As you increase the number of patients, however, your activity could appear to be human research.”\footnote{Mah email to Dr. Schrot, copying Dr. Muizelaar, dated \textit{[blank]}, 2010, Exhibit 124.} Mr. Mah also refers Dr. Schrot to FDA guidelines issued since their last discussion pertinent to the issue and noting, “With this new information, I believe the use of the bacteria would (in FDA’s eyes) be subject to their regulation, purview and authority. (None of this addresses potential California state issues).” He lists a cite to the new FDA guidance and links to that guidance in his email. Mr. Mah then writes: “If you choose to administer the locally-grown bacteria to this second patient in the course of your practice of medicine and in your best judgment as the patient’s treating physician, I would again obtain surgical consent from the subject and/or family…As with the first patient, I recommend you consult with Chief Medical Officer Al Siefkin prior to performing the procedure.” He adds, putting in bold, \textit{“Finally, the caveat: if you anticipate another future patient will need this unconventional/innovative treatment, I recommend a treatment IND application be submitted to FDA and the protocol undergo IRB review, as appropriate, prior to the next procedure.”} (Emphasis in original). He concludes by offering to direct Dr. Schrot to UCD resources to assist with any such IND application.

\textbf{2010:} Dr. Schrot replies to Mr. Mah, copying Dr. Muizelaar, noting that “We completely agree that continued treatment should involve IRB approval in the context of a clinical trial, and we would absolutely like to move forward with
conducting a pilot study.” He states that he reviewed the draft FDA guidelines that Mr. Mah had provided. Dr. Schrot then explains the proposed procedure and states: “We are not implanting an engineered strain of bacteria. The surgery we are performing is otherwise routinely performed for recurrent glioblastoma. We are altering our technique in such a way that the wound becomes contaminated, both by introducing wild type bacteria and by not giving pre-operative antibiotics.” He also notes, “Nevertheless, it could be that, by extension, our proposed study would be considered to be a challenge study by virtue of ‘altering the structure or function of the body,’ and as such, would be regulated. Is it your understanding that we would still need to proceed with an FDA IDE treatment application? If so, what is the next step and what resources are available at UCD to assist with this process?”

/2010: Mr. Mah responds to Dr. Schrot, copying Dr. Muizelaar, indicating that “the FDA has become more aggressive with IND and investigational devices. For that reason, I think an IND is sensible or at very minimum, you obtained documentation from the FDA that no IND is needed. I believe a treatment IND is appropriate here.” (Emphasis added.) He concludes noting that he will introduce Dr. Schrot to Kate Marisuna of CTSC to assist with an IND application.

/2010: Dr. Schrot emails [redacted] asking [redacted] to prepare bacteria for the procedure on Patient 2, noting: “I have discussed the case with the director of the UC Davis IRB and he has given us cautious clearance to do this. After this, we will need an IND from the FDA to further proceed with clinical work. The rat data will be crucial in making such an application to the FDA.” (Emphasis added.)

/2010: Patient 2 and [redacted] review and sign a special consent form that contains the similar disclosures to those provided to Patient 1.

/2010: Dr. Muizelaar performs the procedure on Patient 2. Dr. Schrot is listed as a surgeon for the procedure on the UC Davis Health System file but has informed

58 Dr. Schrot email to Mah, copying Dr. Muizelaar, dated [redacted], 2010, Exhibit 125.

59 Id.

60 Dr. Schrot email to [redacted], dated [redacted] 2010, Exhibit 126.

61 Consent form signed and dated [redacted], 2010, Exhibit 128.

62 Medical record for Patient 2, dated [redacted], 2010, Exhibit 127.
the fact-finder for this investigation that he did not perform or assist with the surgery. Dr. Azeem Oladunjoye is listed as an assistant surgeon in the medical records.

2010: Patient 1 dies, approximately five (5) weeks after surgery. The medical records and information available indicates that the cause of death was consistent with progressive glioblastoma.

2010: Sometime after Patient 2’s procedure, Dr. Muizelaar sees Dr. Fred Meyers at a faculty reception at the Dean’s Suite on the 3rd floor of the Medical Education Building. Dr. Muizelaar is enthusiastic about the proposed procedure using the bacterial infection procedure given Patient 2’s progress and tells Dr. Meyers about it. Dr. Meyers tells Dr. Muizelaar that he needs IRB approval to conduct the procedure. They discuss, among other things, that Dr. Muizelaar will not be able to publish any results of the procedures if he does not have IRB approval. Dr. Muizelaar indicated that he disagreed, but Dr. Meyers tells Dr. Muizelaar that he needs IRB approval.

2011: Dr. Schrot and Dr. Muizelaar sign and file a Record of Invention (“ROI”) for the bacterial intervention procedure with the Technology Transfer Services at UCD. In the ROI, they explain: “Purified cultures of Enterobacter aerogenes are obtained from ATCC and allowed to grow overnight in Luria broth at 37°C. The treatment is applied during a craniotomy surgery for recurrent glioblastoma.”

2011: Dr. Muizelaar informs Dr. Siefkin about the procedure on Patient 2 and that he is doing very well and that he had not obtained IRB approval as Dr. Siefkin had asked. Dr. Siefkin is surprised and disappointed that Dr. Muizelaar had performed the procedure without IRB approval and tells Dr. Muizelaar not to do any additional cases. They discuss that this was not an approved protocol and Dr. Siefkin informs Dr. Muizelaar that he needs to get support from the IRB and needs IRB approval to do any additional cases.

Dr. Muizelaar stated in his interview that he believed this was after Patient 3. Given the evidence regarding the timing regarding the procedure conducted on Patient 3 and the aftermath thereafter, it appears more likely that Dr. Meyers’ recollection is correct.

Interview of Dr. Fred Meyers, November 16, 2012.

ROI dated [redacted], 2011, signed by Dr. Muizelaar and Dr. Schrot, Exhibit 130.

Dr. Siefkin email to Dr. Muizelaar, copying Dr. Schrot, Anna Orlowski, Leslie Navarra, James Kirk, Dr. Fred Meyers, Linda Ham and Teresa Porter, dated [redacted], 2011 (summarizing past events), Exhibit 143.
Patient 3, [redacted], with no previous radiation or chemotherapy, arrived at the emergency room with complaints of multiple symptoms. A CT scan reveals a large right temporal mass, suspicious for glioblastoma. On or about this date, Patient 3 meet with Dr. Muizelaar who discussed [redacted] options for treatment with Patient 3 and [redacted]. According to a Memorandum later prepared by Dr. Muizelaar and Dr. Schrot for Dr. Siefkin, “Because of the highly encouraging results [they] had seen in case #2, and given the grim prognosis associated with the best current standard therapy, [they] felt ethically obligated to discuss [their] recent experience with cases 1 and 2 with the patient and family.”

An undated Consent form, entitled Additional Consent for Surgery for [Patient 3] is signed by Patient 3 and [redacted] and Dr. Schrot. The form contains many of the same statements as those in the forms for Patient 1 and 2. However, it also states that the procedure had been “tried by the surgeons twice in the past year, and that one patient died from disease progression, and that the other patient seems to be improving with signs of tumor regression.” In addition, it states: “We are aware that the bacteria to be implanted come from the brain tumor animal laboratory of Dr Schrot, and have not been tested or certified by the FDA or any other Federal or State agency.” It also states: “We grant permission for Drs. Muizelaar and Schrot to publish any information learned in the course of this clinical treatment option. We understand that this treatment option is not currently part of a clinical trial, and that this treatment method has not been subject to FDA approval or IRB review, but represents the best clinical judgment of Drs. Muizelaar and Schrot, who are solely responsible for its use in this particular case.”

Dr. Muizelaar performs the procedure Patient 3. Dr. Schrot is listed as the assistant surgeon on the medical record, as is Dr. Huy Duong. Dr. Schrot has informed the fact-finder that he did not conduct the surgery on Patient 3 and in fact was not present for any part of the surgery.

Dr. [redacted] affiliated with [redacted], emails Dr. O’Donnell and Dr. Schrot regarding another patient with glioblastoma; [redacted] notes that the patient’s [redacted] worked at [redacted] in the past on a bacterial infection model to stimulate the immune system and contacted Dr. Muizelaar “about his infection of the

67 Memorandum, undated, prepared by Dr. Muizelaar and Dr. Schrot, Exhibit 131.

68 Undated Consent form signed by Patient 3 and [redacted], Exhibit 132.

69 Medical Record for Patient 3, dated [redacted], 2011, Exhibit 134.
CONFIDENTIAL

cavity/bone flap model in GBM.” further notes that has had a long discussion with the family about the risks and that they are interested in a consultation to discuss treatment options.

/2011: Intellectual Property Officers Randi Jenkins and Raj Gururajan of UCD Technology Transfer Services meet with Dr. Muizelaar and Dr. Schrot to discuss the ROI that they submitted. Mr. Gururajan recalls that during the meeting, they discuss the invention, the ethics of patenting medical procedures and the possibility of the inventors creating composition of matter with respect to specific bacterial cultures in the future could be possibly be patentable subject matter, depending on what the inventors would invent. Regarding the ethics of patenting medical procedures, it is the American Medical Association’s position that it is unethical to patent inventions that are solely medical procedures. For that reason UC does not file patent applications on inventions that are strictly medical procedures. Although these issues were discussed, a decision whether to submit a patent application regarding the ROI submitted by Dr. Muizelaar or Dr. Schrot was not made at the meeting.

/2011: Dr. Muizelaar asks Karen Smith, RN, to assemble an “ad hoc Ethics Committee” to consider a proposal to treat 4 or 5 additional glioblastoma patients with the wound infection procedure. The proposed ad hoc Ethics Committee put together by Karen Smith is: Praveen Prasad MD (Sutter neurosurgeon and member of UCDMC ethics board), Karen Smith RN, Stu Cohen MD (UCDMC Infectious Diseases), and Robert O’Donnell (UCDMC neuro-oncologist).

/2011: Dr. Schrot prepares a Prospectus addressed to the ad hoc Ethics Committee regarding the proposal, with input from Dr. Muizelaar. The Prospectus states in part, “Thank you for agreeing to serve on this ad hoc Ethics Committee at the behest of Fred Meyers, MD, MACP, Executive Associate Dean of the UC Davis School of Medicine.”

Dr. Meyers strongly denies ever suggesting review by an “ad hoc Ethics Committee,” and states that he “absolutely” did not make this recommendation as represented in the Prospectus.

---

70 exhibit to Dr. Schrot and Dr. O’Donnell, dated 2011, Exhibit 135.

71 December 6, 2012 interview of Karen Smith.

72 2011 Prospectus submitted by Dr. Schrot and Dr. Muizelaar, Exhibit 136.

73 November 16, 2011 interview of Dr. Fred Meyers.
The Prospectus also states: “this ad hoc Ethic Committee has been assembled to make a recommendation to the Dean and/or IRB administration regarding the ethics of urgently treating this patient in the absence of a formal IRB protocol and also, by extension, treating several other glioblastoma patient (no more than 5) who request this treatment.” In the section entitled “Regulatory Issues” in the Prospectus, it states, in part: “We feel however that enlisting the endogenous organism E. aerogenes cultures to create an intentional surgical wound infection lies in a grey area in terms of FDA regulation…Nevertheless, we are using E. aerogenes in a specific way to treat a malignant glioblastoma, and we will develop a formal clinical research trial protocol in the near future. We will explore the need for an IND application to accompany a formal IRB-approved clinical trial at that time.” (Emphasis in original.)

/2011: Although the ad hoc Ethics Committee never meets or discusses the Prospectus, Karen Smith emails Eric Mah and members of the committee, identifying the committee members: “We have reviewed the Prospectus developed by Rudolph J. Schrot, MD, MAS and J. Paul Muizelaar, MD, PhD and believe it to be a reasonable treatment for glioblastoma. We would recommend continuing this informal clinical activity to include an additional 5-6 patients with the understanding that an IRB-approved formal protocol be developed as soon as possible.” The email notes: “Please feel free to submit additional comments. We will be meeting with Eric C. Mah, Director of IRB Administration and the Chair of an IRB Committee on Wednesday, 2011.…”

/2011: Dr. Schrot schedules a meeting with Mr. Mah and Dr. Anderson to discuss the Prospectus. Dr. Schrot sends a follow-up email noting the date and location of the meeting to Dr. Anderson, copying Mr. Mah, Smith and Dr. Muizelaar.

/2011: Mr. Mah responds to Dr. Schrot’s email, noting that he has invited Dr. Asmuth, an IRB Co-Chair, to attend the meeting as well.

Karen Smith confirmed in her interview that despite the language used in her email, the ad hoc Ethics Committee never met or discussed the Prospectus. Dr. O’Connell and Dr. Muizelaar confirmed the same in their respective interviews. See also October 4, 2012 letter from Dr. Muizelaar and Dr. Schrot at p. 15, Exhibit 168 (“We scheduled a meeting with the IRB administration before any of the individuals had responded to the letter [Prospectus]. There was therefore no opportunity for this ad hoc group to meet prior to our meeting with the IRB administration.”)

Smith email to Mah, Robert O’Donnell, Stuart Cohen, Praveen Prasad, copying Dr. Schrot and Dr. Muizelaar, dated 2011, Exhibit 144.

Schrot email to Dr. Anderson, copying Smith, Mah and Dr. Muizelaar, Exhibit 138.
Mr. Mah meets with Dr. Muizelaar and Dr. Schrot to discuss Prospectus. Dr. Asmuth, and Karen Smith also attend the meeting. At the meeting Dr. Muizelaar reports that Patient 3 is not doing well. Mr. Mah communicates to Dr. Muizelaar and Dr. Schrot that they may not conduct the procedure on any other patients at this time.

Patient 3 dies, two weeks after the surgery. 78

Dr. Schrot emails Mr. Mah, noting: “Thanks for meeting with us yesterday to discuss the FDA requirements. I would like to move forward with applying for an IND to use intracranial E. aerogenes for recurrent treatment refractory GBM. You mentioned you had some contacts who would be helpful in this regard.” 79

Mr. Mah responds to Dr. Schrot’s email, asking him to give him a call or provide a number at which he can reach him.

Mr. Mah emails Dr. Schrot, copying Dr. Muizelaar, Dr. Asmuth, and Dr. Anderson: “As a follow up to our meeting yesterday, please confirm (by replying to this email) your agreement to cease all activities using the probiotic treatment. Any additional activity will require review by the IRB and/or IRB Chair.” The subject line of the email is “Cease and Desist: Probiotic Treatment.”

Mr. Mah initiates an IRB investigation to determine whether the actions of Dr. Muizelaar and Dr. Schrot in manufacturing and administering the product constituted serious and/or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB. 80

Dr. Siefkin emails Dr. Muizelaar, copying Dr. Schrot and others, after learning that Dr. Muizelaar has performed a third case of the implantation of bacteria into

( . . . continued)

77 Id.

78 Medical record for Patient 3, signed by Dr. Krista N. Keachis, dated [redacted], 2011, Exhibit 139.

79 Dr. Schrot email to Mah, dated [redacted], 2011, Exhibit 140.

80 Confidential IRB Memorandum summarizing findings of IRB investigation, dated August 31, 2011, Exhibit 151.
the brain of a patient with glioblastoma.\textsuperscript{81} The email details past discussions between Dr. Siefkin and Dr. Muizelaar, noting that \textbf{after the procedure was conducted on Patient 2}, Dr. Siefkin told Dr. Muizelaar “not to do any additional case.” He notes, “I regret I did not write to you after our meeting second meeting [sic], but I was certain you understood you needed IRB approval to proceed to do additional cases…You have now done a third case. The Chief Compliance Officer notified me that you have not obtained IRB approval and you are potentially in violation of a number of University and Federal regulations. You also did not follow my instructions to you.” Dr. Siefkin then provides a list of instructions to Dr. Muizelaar in all caps, including: “DO NOT SEE ANY ADDITIONAL PATIENTS IN EVALUATION FOR THIS PROCEDURE! IF YOU HAVE ALREADY STARTED SEEING THEM, STOP! DO NOT PERFORM ANY ADDITIONAL SURGERY ON ANY PATIENTS USING THIS PROCEDURE!….” (Emphasis in original.) Additionally, Dr. Siefkin notes that there will be a Peer Review committee meeting scheduled for April 18 to discuss the cases.

\textbf{10/2011:} Mah seeks assistance from Chief Compliance Officer Teresa Porter regarding IRB investigation. Porter assigns investigator Gina Guillaume-Holleman to assist with investigation.\textsuperscript{82}

\textbf{10/2011:} Dr. Muizelaar emails Dr. Siefkin in response to Dr. Siefkin’s \textsuperscript{\textbullet} \textsuperscript{\textbullet} email.\textsuperscript{83} He writes in part: “I understand the commotion this has caused all of you, but I don’t think anybody has done anything ‘wrong’ to this point. Moreover, both cases 2 and 3 were discussed with deans Meyers and/or Pomeroy and/or Goodnight. Before embarking on further cases, Fred and Jim advised me to get a little ‘outside’ committee together to advise the IRB on how to proceed further, including an ethical board member….We met with the IRB’s Dr Mah [sic] on \textsuperscript{\textbullet} \textsuperscript{\textbullet} 11, and it was decided to try to get an IND from the FDA for patients with a recurrent malignant brain tumor in whom conventional therapy has failed. We also agreed to not do any further cases until such IND has been obtained. I still think that the use of native bacterial cultures for intentional wound infection falls into a gray area of FDA oversight, and is clearly subject to interpretation…The use of bacterial cultures, although originally obtained from the

\textsuperscript{81} Dr. Siefkin email to Dr. Muizelaar, copying Dr. Schrot, Anna Orłowski, Leslie Navarra, James Kirk, Dr. Fred Meyers, Linda Ham and Teresa Porter, dated \textsuperscript{\textbullet} \textsuperscript{\textbullet}, 2011, Exhibit 145.

\textsuperscript{82} October 24, 2012 interview of Guillaume-Holleman.

\textsuperscript{83} Dr. Muizelaar email to Dr. Siefkin, copying Anna Orłowski, Dr. Meyers, James Kirk, Linda Ham, Leslie Navarro, Dr. Schrot, and Teresa Porter, dated \textsuperscript{\textbullet} \textsuperscript{\textbullet}, 2011.
CONFIDENTIAL

ATCC in Manassas, VA, have been maintained for over a year in Dr [sic] Lorena Navarro’s lab on campus, so the actual organisms were completely ‘home grown’ and have no crossed state lines….” Dr. Muizelaar signs the email, “Paul (with full agreement of Rudy)”.  

2/2011: An autopsy is performed on Patient 3 which determines that the cause of death was attributed to (1) glioblastoma; (2) meningitis, and (3) anoxic changes.  

2/2011: Dr. Muizelaar and Dr. Schrot prepare Memorandum in response to the request by Dr. Siefkin, summarizing the three cases.  

2/2011: Medical Staff Peer Review Committee meets and discusses the procedures conducted on the three patients with Dr. Muizelaar and Dr. Schrot.  

2/2011: Medical Staff Peer Review Committee issues memorandum to Dr. Muizelaar and Dr. Schrot regarding the Committee’s findings and determinations.  

8/31/2011: Dr. Asmuth reviews the draft IRB report prepared by Mr. Mah and sends a response that notes, “the physician also removed tissue from the brains of patients to perform special stains, disseminated this information to the degree that a fourth patient from an outside hospital had been referred to them for this treatment. This

---

October 24, 2012 interview of Gina Guillaume-Holleman.
is what prompted their approach to the IRB because the referring physician was requesting IRB approval for their experimental therapy."  

2011: Mr. Mah emails results of Confidential IRB investigation findings to Dr. Schrot and Dr. Muizelaar, copying others. Mr. Mah notes, “As part of this process, you may provide written comments to the report which will be reviewed at the September 7, 2011 meeting.” The findings contain a chronology of facts as determined by the IRB, a section on the physicians’ perspective, and note that the IRB must determine whether “serious and/or continuing noncompliance with FDA regulations or the requirements of the IRB occurred.” It further notes that Dr. Muizelaar and Dr. Schrot were provided with the report and will have the opportunity to make comments at the IRB meeting scheduled for September 7, 2011.

9/7/2011: IRB Committee B holds meeting to review and discuss Investigation Report.

9/16/2011: IRB issues confidential letter to Dr. Muizelaar and Dr. Schrot. The IRB determines that: (1) for Patient 1, although the treatment of Patient 1 with the bacteria in the course of practice may not have constituted human subjects research, incorrect information was provided to the IRB concerning the source of the bacteria, which was in fact from ATCC and was designated not for human use; and (2) administering the bacteria to Patient 2 and 3 constituted human research without IRB approval in violation of Policy 240 and other established procedures and institutional requirements. The IRB then instructs the surgeons not to use the bacteria or perform the procedure without IRB and FDA review and authorization and sets other limits on their ability to conduct human research.

9/21/2011: David Segal, Chair of the UCD Institutional Biosafety Committee (“IBC”), sends letter to Dr. Schrot stating that the IBC determined that Dr. Schrot’s use of

86 Asmuth email to Mah, Dr. Anderson, and others, dated August 30, 2011, Exhibit 148.

87 Mah email to Dr. Schrot and Dr. Muizelaar, copying Elodia Tarango, and Silvia Hughes, Exhibit 150.

88 Dr. Muizelaar and Dr. Schrot have argued that: “At no time are Drs. Muizelaar and Schrot invited to address the IRB directly.” (October 4, 2012 Muizelaar and Schrot letter at p. 18, Exhibit 168.) Mah has stated that they were given multiple opportunities to submit comments to the IRB and that they never asked to speak to the IRB, which is not the common practice in any event.

89 Letter from Dr. Asmuth and Dr. Anderson, Co-Chairs of IRB, to Dr. Muizelaar and Dr. Schrot, dated September 16, 2011, Exhibit 153.
infectious agents obtained and cultured as approved under a Biological Use Application 0878, for a purpose for which he had not obtained approval via a BUA amendment or new BUA, constitutes a violation of the terms and conditions of Dr. Schrot’s BUA and the policies in UC Davis Policy and Procedure 290-55 (biological safety). Dr. Segal notes that the IBC thus requires Dr. Schrot to, *inter alia*, permanently cease all work under BUA 0878, destroy all stocks of *Enterobacter aerogenes*, including those originally obtained from ATCC, euthanize all animals used in the studies.

9/26/2011: Dr. Muizelaar and Dr. Schrot submit a letter to the IRB to respond to the IRB’s findings, stating: “We have reviewed the findings of the IRB investigation and offer the following additional comments to provide a context to the facts as outlined.” The letter explains that they understood that the procedure on Patient 2 “was authorized by the IRB Director, who additionally provided a recommendation for a treatment IND and IRB review for any additional cases beyond the second case.” With regard to Patient 3, they state that “This case had not been directly authorized by the IRB Director. Our understanding at the time was that although a treatment IND with IRB review for additional (> 2) cases was indeed previously recommended by the Director (Email #2), this was a recommendation but not necessarily a requirement.” They further comment: “We no longer believe that application of bacteria to create an intentional wound infection falls outside the purview of the IRB and FDA, nor that the bacteria cultured for over a year in a UC Davis laboratory, but originally derived from Manassas, VA, are considered ‘locally obtained.’” Further refinements in our understanding of the regulatory requirements include the necessity of producing the biologic in a GMP facility. Dr. Schrot met with Gerhard Bauer to discuss this on July 12th, 2011.”

9/21/2011: IBC issues decision to Dr. Muizelaar requiring that he cease all work authorized under Biological Use Authorization (“BUA”) 0878, destroy all stock of the

---

90 Exhibit 154.

91 The letter is undated; according to Dr. Muizelaar and Dr. Schrot, this response to the IRB was sent on or about September 26, 2011. *See* October 4, 2012 Muizelaar and Schrot letter at p. 18, Exhibit 168.

92 More recently, Dr. Muizelaar and Dr. Schrot have stated: “We wrote at the time that we felt this innovative treatment would fall within in the purview of the IRB and FDA, but in hindsight, looking deeper into this matter, we have changed our mind. The innovative treatments rendered should not require IRB approval.” *See* October 4, 2012 Muizelaar and Schrot letter at p. 18, Exhibit 168.
bacteria, euthanize all animals used in the studies under BUA 0878, properly dispose of all waste, provide a letter to IBC documenting those actions.  

10/14/2011: IRB issues summary of decision, noting: “After due consideration by each of the IRB biomedical committees, the IRB reaffirms its initial determination that the surgical procedures to treat glioblastoma with intentional wound infection were undertaken without IRB review and approval and that these activities constitute serious and continuing non-compliance with University policies and federal regulations.”

10/17/2011: UCD Office of Research, Vice Chancellor for Research Harris A. Lewin, notifies the FDA of “serious and continuing noncompliance” associated with the use of a biologic by Dr. Muizelaar and Dr. Schrot to treat three glioblastoma patients.

10/21/2011: Office of General Counsel issues a research advisory regarding the emergency “compassionate” use of unapproved drugs, which is distributed to the IRB and Compliance Department.

3/22/2012: The Innovative Use Policy is published, providing guidance and support to physicians for the innovative use and novel application of medical therapies, devises, and/or medications in the treatment of patients.

11/13/2012: California Department of Health & Human Services, Centers for Medicare & Medicaid Services issues a letter to UCD Medical Center noting that Department of Public Health (“CDPH”) reported serious deficiencies from the August 30, 2012 compliant validation survey of the hospital (“CMS Report”), Exhibit 169. The letter notes that UCD Medical Center is being placed under the CDPH survey jurisdiction until it demonstrates full compliance.

---


94 Tarango email to Dr. Muizelaar and Dr. Schrot, dated October 14, 2011, attaching IRB determination letter, signed by Dr. Asmuth and Dr. Anderson, Exhibits 157-158.

95 Letter from Vice Chancellor Harris Lewin to Patricia A. Holobaugh, U.S. Food and Drug Administration, dated October 17, 2011, Exhibit 159.

CONFIDENTIAL

12/6/2012: Chief Medical Officer Siefkin responds to the reported deficiencies noted in the CMS Report, in pertinent part: “While we agree that the surgeons did not obtain appropriate approvals from the Institutional Review Board and/or the Medical Staff for the second and third cases, we also believe that all of these surgical cases were physician-driven efforts to prolong the patients’ lives. These surgical cases involved the use of an unmarketed biologic and did not constitute ‘research,’ and therefore this did not fit squarely within then-existing policies and procedures governing human subject research and did not involve the delivery of investigational drugs or devices into the surgical setting...” Exhibit 169.

VIII. ADMINISTRATIVE FACT-FINDING

A. Interview of Dr. John Anderson

Dr. Anderson has served on the IRB since 1999. He has been the Chair of one of the clinical committees, Committee B, since 2004. He explained that the IRB is responsible for all human research—whether at the medical center or campus. Committee A and B generally handle the same type of issues; a researcher submits an application to the IRB and then the application is assigned to either Committee A or B. He said that the role of the IRB is to maintain the public trust—where a procedure could be scrutinized, the IRB provides further oversight.

Dr. Anderson first heard of the proposed procedure when he received an email from Dr. Schrot in 2008 regarding the patient. He vaguely recalls telling Dr. Schrot that he should contact the FDA about the treatment. He also recalls speaking with Dr. Asmuth and the IRB director about the proposed procedure shortly thereafter.

Dr. Asmuth had expressed concern about procedure from his perspective an infectious disease expert. Dr. Anderson was more concerned about the lack of background information about the proposed treatment and that the evidence supporting its use was anecdotal. He said that he thought there were some “red flags” regarding the procedure, so he referred Dr. Schrot to the FDA.

We asked him to explain his understanding (as IRB Co-Chair) of “research” vs. “innovative treatment.” He explained that the FDA has strict guidelines and the IRB generally follows the federal definition of “research,” but that there are shades of gray. He said, for example, use of a drug that has already been approved for other purposes is common and is not research. But use of an unapproved drug could be research because it is investigational. It may not be human research, but it should still be reviewed by the IRB. Additionally, he said that if something meets at least one definition of human research, even if it is not the FDA’s definition, it should be reviewed by the IRB.

When asked him about his email dated 2008 regarding the potential for having the treatment “go forward without full committee final approval (assuming the FDA doesn’t have expressed problems with this).” He explained that he was trying to determine the urgency of the
procedure—how quickly did this truly need to be done? The IRB meets every week and there can be a full committee review within a few weeks. Ultimately, the FDA did express concern in 2008, so the IRB would not have approved the procedure with or without full committee review by the IRB.

After the patient case in 2008, Dr. Anderson was later asked to consult on Patient 1 on a critical care issue unrelated to the surgery. He does not recall what he thought about it at the time. He next learned about the issues after the IRB was informed about the procedures after Patient 3, when Mah notified the IRB committee. He was invited to attend a meeting with Mah and others, but was unable to attend.

Later, Dr. Anderson did participate in an Executive Committee meeting of the IRB where the cease and desist letter was discussed. Mah said at that meeting that Dr. Muizelaar and Dr. Schrot treated more patients than he had expected. The IRB ultimately determined that Dr. Schrot and Dr. Muizelaar were not in compliance with FDA regulations.

Dr. Anderson noted that he was an IRB Co-Chair during the period Patients 1, 2, and 3 received treatment. Since Dr. Schrot had discussed the issue with him in 2008, he was surprised that Dr. Schrot did not go to him again when they later wanted to perform the procedures in 2010. He had educated Dr. Schrot about the FDA regulations in 2008, but Dr. Schrot did not seek his advice later.

When asked what, as IRB Co-Chair, he thought about Dr. Muizelaar and Dr. Schrot’s position that the statement by Mah regarding Patient 2 was just a “recommendation” not a requirement, he said he was not sure what Mah specifically told them. But he said that they knew it was controversial in 2008, and questioned how could it not be controversial in 2010. In his opinion, the 2008 advice about FDA approval was still applicable in 2010.

He also noted that the patients were considered a vulnerable population (because of their terminal illness), which is why there is also the need for additional procedures in obtaining consent. He said there are limitations on the ability of researchers to conduct research vulnerable populations like children, pregnant women, and prisoners. But he said that with additional safeguards, he would expect the patients could consent.

Dr. Anderson also noted that “research” under federal law is systematic research for generalized knowledge—getting at multiple procedures versus a single one. However, he said that even with single patient, the procedure was “experimental.” Also, he said that something that might even be considered research should go the IRB. He said that anyone that wants to do research is given training (Dr. Anderson noted he has given several talks on this) and should be aware of the requirements.
B. Interview of Dr. David Asmuth

Dr. Asmuth started serving on the UCD IRB in 2002; he served as the UCD IRB Co-Chair from 2005 until April 2012. He worked with several IRB directors during that time frame. Dr. Asmuth said that he is an HIV researcher and an infectious disease specialist—so ethics and human research, is a large part of his work. In April 2012, Dr. Asmuth was hired as the Head of Research at the VA. When asked for more detail about the IRB, Dr. Asmuth explained that there is no real distinction between Committee A and B, they work together but divide the protocols that need to be reviewed. He said that each committee reviews about 15-25 protocols per meeting—most of these are renewals, but approximately 5-10 of the protocols are new proposals.

In 2008, he learned about the proposed procedure via his role as IRB Co-Chair from pediatric ethicist Dr. Alex Kon. Dr. Asmuth’s impression at that time was that it was an experiment, not a best practice, and that Dr. Schrot and Dr. Muizelaar needed to proceed with the appropriate clinical work first. He told this to Dr. Anderson, who communicated this to Dr. Schrot at that time. Dr. Schrot agreed and later started the rat tests with the help of a graduate student.

Dr. Asmuth said that in 2008 there was some pressure to do the procedure as a single treatment, emergency procedure—but he said at the time that full committee review of the IRB was required. The alternative would have been for the doctors to state that this procedure was not research, which was what Dr. Schrot apparently did when the issue was later revived. Dr. Asmuth said that he believed that they argued it was innovative care to go the non-research route, since the IRB has no oversight over innovative care.

He said that the determination in 2008 was that this procedure was research, not innovative care. Dr. Asmuth noted there was no literature to support the procedure. There was some case data to support animal model—but not sufficient data to support human procedure. Dr. Anderson agreed with Dr. Asmuth’s assessment—and Dr. Asmuth said that they clearly told Dr. Schrot he needed to get an IND if this came up again.

Dr. Asmuth directed Dr. Schrot and Dr. Muizelaar to Skip Nelson (a pediatrician) at the FDA. An IND is obtained through FDA. For something new such as this, FDA will require extensive, preclinical data. Dr. Asmuth did not believe IND could be obtained at this point, but knew they needed to start the pre-clinical work (obtain bacteria type, colony count, application, etc.) Dr. Asmuth said that the proposed procedure was so experimental and unusual, he did not think an IND would be obtained. He expressed his belief that this is why Dr. Schrot and Dr. Muizelaar later circumvented IRB.

He also said that the 2008 FDA response, when it denied Dr. Schrot’s request, makes Dr. Schrot’s later statements not credible. Dr. Schrot knew that animal testing and pre-clinical work were required and Dr. Asmuth told him to fill out a full committee application. Dr. Asmuth said he was telling Schrot it was research—which is why he said they needed to submit a full committee application.
When asked why he believed this was procedure was research and not innovative care, Dr. Asmuth said it was because there was no body of literature to support the procedure. They only had a few case reports that would support doing it on an animal model—this was not sufficient to support for use in humans.

In 2010, when they went to Mah for the single case, Dr. Asmuth said he felt that this was a go-around, because he would not have agreed to allow them to circumvent the IRB.

In March 2011, he learned that the procedures had been performed on Patients 1, 2, and 3; he was surprised and incredulous that Dr. Schrot had come back and made same argument that was rejected in 2008. He explained that Mah’s determination on the proposed single patient treatment was significant because the criteria are specific that if there is more than one case, IRB review is necessary.

Dr. Asmuth does not recall discussing the issue regarding the source of the bacteria in 2008 but he agreed that innovative use can only occur if the product was local. If the product was from out-of-state, it would automatically become FDA regulated product requiring IRB review. He believes that “home grown bacteria” would have to have been cultured from wound or blood, must be a clinical specimen, not from ATCC.

We showed Dr. Asmuth the statement in the October 17, 2012 letter from Dr. Muizelaar and Dr. Schrot at page 17 that states: “The determination that bacteria from a local laboratory are not in fact local if the seed cultures are from the ATCC is unprecedented, and flies against the advice previously given by Dr. Skip Nelson and David Asmuth in 2008.” Dr. Asmuth replied that he disagreed with the statement and that he never gave that advice.

He then stated that the origin of the bacteria is a red herring—the origin of the bacteria is irrelevant when it when it comes to Dr. Schrot’s activity because he was fully aware of what was required before he started any human procedures. Dr. Asmuth stated that Dr. Schrot was clearly told to start animal experiments and this was put into motion.

Dr. Asmuth attended the [redacted] 2011, meeting with Dr. Muizelaar, Dr. Schrot, and Mah. He could not recall if Karen Smith was present. The meeting was at CTSC in a conference room across from the IRB. Dr. Schrot led the meeting and described what had happened and the Prospectus. He said they wanted to enroll more patients in a “clinical trial.” He said that he and Dr. Muizelaar had been discussing it with colleagues and that an outside physician had a patient who wanted to enroll, but the physician wanted to see an IRB approval number. Dr. Asmuth said the need for the IRB number was Dr. Schrot and Dr. Muizelaar’s motivation for going back to Mah. During the meeting, Dr. Schrot and Dr. Muizelaar described issues samples, interactions with patients, consent forms, and continued to characterize the procedure as innovative care and not research.
CONFIDENTIAL

Dr. Asmuth said that Dr. Muizelaar did not say much at the meeting; Dr. Schrot was doing most of the talking. He has heard suggestions that Dr. Muizelaar was behind everything, but Dr. Asmuth’s observation was that Dr. Schrot was “driving it.” It appeared that Dr. Schrot had prepared all materials, and the animal experiments and graduate student were all under this direction—in his lab. Dr. Asmuth said that it became apparent at the meeting that Dr. Asmuth and Mah were not agreeing with Dr. Muizelaar and Dr. Schrot. They (Asmuth and Mah) determined that they would need to send cease and desist letter, and contact FDA and other University authorities.

When asked whether he thought it seemed like Dr. Muizelaar and Dr. Schrot had a different understanding of the definition of research, Dr. Asmuth said he did not think so. He said Dr. Schrot and Dr. Muizelaar are on many IRB protocols and have undergone training; he believes they were aware of the definition of research, which is why they called their proposal a “Prospectus” and not Protocol.

For the subsequent IRB investigation, Mah as the Director took the lead. Dr. Asmuth did not have any discussions with Dr. Sieffkin about the matter.

Regarding other issues, Dr. Asmuth said that there were issues with handling of the bacteria. He said that there is a protocol for bringing a biologic into the OR.

Additionally, Dr. Asmuth stated his belief that Dr. Muizelaar and Dr. Schrot should be banned from research. The IRB deliberated this at two separate meetings. He had also heard (at a much later date) that Dr. Sieffkin had told Dr. Muizelaar to stop after Patient 2, but Dr. Schrot and Dr. Muizelaar conducted the procedure again anyway.

After the interview, Dr. Asmuth forwarded a few emails to the fact-finder.

C. Interview of Gina Guillame-Holleman

Gina Guillame-Holleman is a Corporate Compliance Investigator for UCD Health System. In March of 2011, she was appointed to assist with the investigation conducted by the IRB regarding potential research misconduct by Dr. Muizelaar and Dr. Schrot. She conducted several interviews for the IRB in connection with this role.

Ms. Holleman interviewed Dr. Schrot for the investigation and requested all communications with the IRB, FDA, and any other relevant agency related to the procedures. Ms. Holleman stated that Dr. Schrot acknowledged that the bacteria used in the procedures was from ATCC but Dr. Schrot told Eric Mah that the bacteria was being “generated” in a home lab. Ms. Holleman further stated that she was informed the bacteria cultures were purchased for the purposes of animal testing. She said that when she questioned Dr. Schrot as to why he did not
complete the animal trials before conducting the treatment on humans, he replied that such
testing would take “10 years . . . his entire career.” Ms. Holleman was concerned with Dr.
Schrot’s eagerness to proceed with use of bacteria in humans and avoidance of procedure; she
found his actions “reckless.” When Ms. Holleman questioned Dr. Schrot about his discussions
with Eric Mah, Dr. Schrot represented that he believed that as a treatment, the proposed
procedures would fall outside IRB review.

Ms. Holleman also interviewed [redacted], the lab assistant responsible for
culturing and transporting the bacteria used for the procedures. [redacted] stated that [redacted]
transported the bacteria to the OR for the procedures in a Styrofoam container and was escorted
into the OR where [redacted] transferred the bacteria to an unknown technician. Ms. Holleman also
interviewed Dr. Robert O’Donnell, an oncologist, who stated that he was concerned that Dr.
Schrot seemed to be conducting research without a proper protocol or IRB approval. He said
that when he asked Dr. Schrot about it, Dr. Schrot told him that he was seeking IRB approval.
Dr. Schrot further requested Dr. O’Donnell’s assistance in developing a protocol but did not
follow up on this request.

Ms. Holleman also interviewed Dr. Fred Meyers, who was of the opinion that the
treatment was “innovative research” and was not aware of the 2008 IRB submissions and
denials. She interviewed Sean Barry, who was concerned with violation of the Material Transfer
Agreement, which provided that the bacteria could not be used in humans.

D. Interview of Dr. Alex Kon

Dr. Alex Kon, a doctor in pediatrics, served as the Chair of the Bioethics Consultation
Committee at UCD in 2008. Before his interview, he asked to review a copy of the Bioethics
Consultation Committee report to refresh his recollection of the events that occurred with regard
to Dr. Schrot’s request for a bioethics consultation for the [redacted] patient in 2008.

Dr. Kon recalls that Dr. Schrot brought the proposed treatment of the [redacted] patient to
the committee, through committee member Ben Leavy in 2008. He recalls that the they were
told that the patient’s [redacted] had heard reports about prolonged survival in glioblastoma patients that
got a wound infection. The patient had a very grave prognosis with no chance of survival.

A meeting was held in the Pediatric Conference Room, with Dr. Schrot in attendance for
at least part of the time. The Bioethics Committee had a great deal of discomfort about the idea.
The consensus was there needed to be oversight and the Bioethics Committee lacked the
necessary resources to ensure sufficient oversight. They determined that it needed to go to the
IRB, which had the mechanism to provide the necessary oversight. The clear sentiment was that
it needed IRB approval.

Dr. Kon vaguely recalls that Dr. Schrot did not view it as research because it was not
something that they would do again; it was a one-time procedure at the request of the family.
But the Committee felt that the neurosurgeons should either develop it as research and get IRB approval or there should be some surgical innovation oversight committee formed at UCD.\footnote{Dr. Kon noted that other universities, such as UCSF and Stanford, have surgical innovation oversight committees to provide oversight and guidance on surgical procedures that are not research. He noted that this is discussed in pediatrics a great deal because there was a new surgical procedure that was being used in heart surgery for years but when the research was conducted on the procedure, it was learned that there was no benefit whatsoever to the new approach. A committee was need to review “innovative” techniques and procedures. Dr. Kon asked Leslie Navarra and Judy Fochs to discuss this need with the Executive Committee.}

When asked whether the Bioethics Committee discussed whether the procedure should be deemed “experimental” (because of the use of the term “experimental” in the Bioethics Consultation Committee’s report) Dr. Kon said that there was not a clear consensus on that term or any real determination about the meaning of the term.

He said the Committee was not opposed to the procedure being done and that there was a lot of sympathy for the patient. The Committee simply did not feel that it was in a position to make the call whether it would be permissible to do the procedure; another body needed to review it and provide more oversight. Performing the procedure was not unreasonable as long as there was sufficient oversight.

E. Interview of Eric Mah

Mr. Mah worked as the IRB Director at UCD from February 2009 until September 2011. Mr. Mah has a master’s degree from John Hopkins School of Public Health and a bachelor’s degree from UCLA. Mr. Mah explained that as IRB Director he oversaw all of the IRB’s committees. In addition to faculty committee members, the IRB had between 9 and 11 staff employees, as well as an Assistant Director. Mr. Mah left UCD on September 3, 2011, when was appointed as Senior Director of Research Compliance at UCSF.

\footnote{Mr. Mah stated in his interview that had he been aware of the animal studies being conducted by Dr. Schrot and Dr. Muizelaar regarding this procedure, it would have changed his analysis regarding whether the procedure for this patient could be considered “research.”}

2010, Mr. Mah received a call from Dr. Schrot requesting authorization for a procedure on a dying patient. Dr. Schrot informed Mr. Mah that the procedure would involve the using live bacteria from his (Dr. Schrot’s) own lab to treat a patient with a rare brain tumor for the purpose of prolonging life. Mr. Mah does not believe that he was aware at that time that a prior request for approval of this treatment had been made in 2008, or that Dr. Schrot was conducting animal studies regarding the proposed procedure.\footnote{Mr. Mah stated in his interview that had he been aware of the animal studies being conducted by Dr. Schrot and Dr. Muizelaar regarding this procedure, it would have changed his analysis regarding whether the procedure for this patient could be considered “research.”}
CONFIDENTIAL

Mr. Mah said that at that time he agreed that Dr. Schrot and Dr. Muizelaar could proceed with the proposed procedure without IRB approval as innovative care given that it was for a single patient and because the surgeons believed it was in the best interest of the patient. Additionally, Mr. Mah thought it was significant that the bacteria that would be used in the procedure was not obtained from an outside source (or across state lines), but rather was from Dr. Schrot’s laboratory at UCD. Mr. Mah sent a follow-up email to Dr. Schrot after their discussions on [redacted], 2010 at 9:57 a.m., which confirmed all of these points. He also noted in the email, “[i]f your intention changes to conduct human subjects research, IRB review and an IND application to the FDA may be required” and he informed Dr. Schrot that “I have consulted with Teresa Porter and she recommends you seek guidance/approval from Chief Medical Officer Al Siefkin.” *Id.*

Mr. Mah stated in his interview that his belief that this procedure was proposed for one patient only was significant to his analysis. He believed that the proposed procedure was allowable under FDA regulations if for a single patient as innovative care. Mr. Mah explained that the designation “innovative care” is rarely used. But he said that if the procedure was going to be performed on a single patient, he did not consider it to constitute “research” under FDA regulations because it would not be systematic.

The next month, in 2010, Dr. Schrot contacted Mr. Mah to inform him about Patient 2 and to inquire whether the procedure could be used in Patient 2. Mr. Mah was surprised to receive this request because he had been informed that Patient 1 presented extremely rare circumstances and Dr. Schrot was making the request regarding Patient 2 only one month later. After a long conversation, Mr. Mah recommended that Dr. Schrot obtain FDA authorization because there was now a proposal to do the procedure on a second patient and the procedure could appear to be human research. Mr. Mah was also concerned because the FDA issued new guidance after the procedure was conducted on Patient 1 that clarified that FDA considers the bacteria that Dr. Schrot and Dr. Muizelaar intended to use on Patient 2 to qualify as a drug. Mr. Mah felt that FDA would consider this procedure using the bacteria to be subject to FDA regulation and authority.

Mr. Mah explained in his interview that although he believed that the bacteria was derived locally when he was discussing Patient 2 with Dr. Schrot, at that point the source of the bacteria was not the deciding factor. Because Dr. Schrot and Dr. Muizelaar were now proposing to conduct the same procedure on a second patient, he believed that it had the appearance of research with a vulnerable patient population. He recommended that they obtain IRB review because the IRB is there to provide objectivity in such cases.

Mr. Mah sent an email to Dr. Schrot, with a copy to Dr. Muizelaar, on [redacted] 2010, confirming the information that he had discussed with Dr. Schrot and providing links to the FDA draft guidance that he had discussed. He also recommended that they consult with CMO Siefkin before the procedure.
Mr. Mah confirmed that he received the email from Dr. Schrot dated [redacted] 2010, in which Dr. Schrot explained his understanding of the FDA guidelines and asked Mr. Mah whether they would still need to proceed with an IND. Mr. Mah responded “I believe IND is appropriate here.” He said this response was consistent with his discussions at the time with Dr. Schrot. He said that he did not have discussions with Dr. Muizelaar but noted that he copied him on email communications.

When asked why Mr. Mah did not use more forceful language in his emails to Dr. Schrot, Mr. Mah explained that he did not view this as his role as IRB Director. He was not in a position to tell doctors how to treat their patients; rather, he believes he had a duty to inform them of the rules.

Sometime in early 2011, Ted Wun, the Assistant Dean of Research, contacted Mr. Mah to inquire about the procedure. Dr. Wun told him that he heard that Dr. Muizelaar and Dr. Schrot were presenting the procedure at Grand Rounds. Mr. Mah responded to the effect that what they were doing was “not ideal”—he viewed this as potentially problematic because if one is presenting on a subject, it could be argued that you are contributing to “generalizable knowledge” (a factor when considering whether something is research). He had a brief discussion with Dr. Wun and told him that they were allowed to use the procedure without IRB approval because it was for a single patient.

Mr. Mah stated that he learned about Patient 3 in [redacted] 2011, when he received the prospectus and the email referring to the Ad Hoc Ethics Committee. He met with Dr. Muizelaar, Dr. Schrot, Karen Smith, Dr. Asmuth and others on [redacted] 2011 for about an hour. At first there was confusion about the purpose of the meeting and why there was an Ad Hoc Ethics Committee being formed. He was told that Dr. Meyers suggested that they form the committee, but Mr. Mah never had a discussion about it with Dr. Meyers.

The tone of the meeting was somber and serious. At this meeting, Mr. Mah learned that there were procedures on more than one patient. Mr. Mah read over the prospectus at the meeting and it strongly implied that Mr. Mah had approved the additional procedures, which upset him because it was untrue and misleading. Mr. Mah explained to Dr. Schrot and Dr. Muizelaar that he was disappointed and angry that this was written and they indicated that they understood; they did not object or claim that Mr. Mah had approved of the procedure on Patients 2 and 3. During the meeting, Dr. Asmuth communicated his belief that the performance of the procedures was egregious and that it overstepped the rights of patients not to be treated as human subjects. Mr. Mah agreed that the procedure on Patient 3 was unjustifiable. They also

---

99 As noted below, Dr. Meyers denies making this recommendation.

100 His reaction to the Ad Hoc Ethics Committee was that Dr. Schrot and Dr. Muizelaar were shopping for approval—they did not want to go to the IRB so it was his impression that they were doing all they could to get around it. They were “looking for a yes” in his opinion.
discussed that Dr. Muizelaar and Dr. Schrot had filed for a potential invention application (Record of Invention) before performing the procedure on Patient 3 and that this was contrary to the “no financial interest” claim in the consent form. By the end of the meeting, it was made clear to Dr. Muizelaar and Dr. Schrot that no further procedures could be performed. Mr. Mah then sent a cease and desist letter to follow-up and confirm.

When asked to respond to claims by Dr. Muizelaar and Dr. Schrot that Mr. Mah said at the meeting, “I didn’t know you treated third patient,” Mr. Mah explained that he meant that he knew they were considering treatment Patient 2, but he did not know that they did so.

When asked to explain his understanding what locally derived bacteria is, Mr. Mah said that local does not include derivatives. When the bacteria is used that has crossed state lines, the FDA has authority. He said he would expect the doctors to know the source of the bacteria.

Mr. Mah confirmed that the IRB initiated a formal investigation, resulting in findings that were sent to Dr. Muizelaar and Dr. Schrot on August 31, 2011. They were given an opportunity to respond to the IRB, which they did. The IRB then met on September 7, 2011 and discussed all of the issues; they later issued an investigation report. The report was sent on October 14, 2011.

When asked to respond to Dr. Schrot’s position that he these were not his patients, Mr. Mah said that Dr. Schrot had told him that he was brought on to specifically assist with innovative care for the patients. He was also always listed as the physician on all of the documents. Mr. Mah said that given Dr. Schrot’s extensive involvement, he never would have known that Dr. Muizelaar was actively involved until someone else had told him. In fact, he said he copied Dr. Muizelaar on some of the emails in 2010 not because he thought Dr. Muizelaar was actively involved, but because he was the Chair of the Department. It was Mr. Mah’s practice to copy the Chair of the Department on unusual cases.

F. Interview of Dr. Fred Meyers

Dr. Fred Meyers is the Executive Associate Dean for the School of Medicine; he said that he runs the operations of the school. Dr. Meyers has not served on the IRB but has utilized the IRB as a director of clinical research.

Dr. Meyers first heard of the wound infection treatment from Dr. Muizelaar at a biannual department meeting with the chairs to review department budgets, recruitment, and initiatives. At this meeting, which may have been as of 2010, Dr. Muizelaar informed Dr. Meyers that he was developing a project related to intentional wound infection, however, Dr. Meyers believed the treatment was still in the “idea” phase.

101 Although Mah left UCD at the end of August 2011 to work for UCSF, he continued to work on the investigation and related issues.
Sometime thereafter, at a reception in the Dean’s suite in the Medical Education Building, Dr. Muizelaar told Dr. Meyers that he wanted to “continue” the intentional wound infection treatment. Dr. Meyers believed there had only been one patient treated at this point and told Dr. Muizelaar that he believed he needed IRB approval to proceed. Dr. Meyers said in his interview that he “distinctly remember saying to him, ‘you need IRB approval.’” He gave Dr. Meyers the clear impression that he wanted to publish the data and Dr. Meyers told him he would need IRB approval to use the data in that way. Dr. Muizelaar disagreed with him about the need for IRB approval, but they did not have any further discussion regarding the treatment. Dr. Meyers never spoke with Dr. Schrot about the treatment.

Dr. Meyers did not remember hearing anything more about it until sometime later, after Patient 3 received the procedure.

Dr. Meyers did not recall informing Dr. Muizelaar that he should pursue an Ad Hoc Ethics Committee to review the treatment and had not seen the Prospectus that was attached to Karen Smith’s email regarding the Ad Hoc Ethics Committee. Dr. Meyers stated that he could not imagine a reason for suggesting an Ad Hoc Committee as this was not standard operating procedure, and he would have in fact recommended against it. Dr. Meyers believed that the treatment was not innovative therapy outside the review of the IRB. He stated that innovative treatment is typically used to allow use of approved drugs for a different purpose than originally intended and that it is not the same as experimentation or clinical innovation. Dr. Meyers was of the further opinion that bacteria that originated outside the laboratory is never considered local.

Dr. Meyers stated that if he had been asked about the Prospectus or the proposed clinical trial, he would have told Dr. Muizelaar and Dr. Schrot to stop and get formal IRB approval. He said he “absolutely” would not have recommended the Ad Hoc Ethics Committee. He noted that these patients are very vulnerable because glioblastoma is fatal; patients in those situations will agree to almost anything. IRB oversight, therefore, was needed. There would be no reason for the Ad Hoc Ethics Committee. He reiterated again that when he talked to Dr. Muizelaar, he was not ambiguous, he told him he needed IRB approval.

G. Interview of Dr. J. Paul Muizelaar

Dr. J. Paul Muizelaar attended medical school in Amsterdam, and following his neurosurgery training and work in Richmond, Virginia and setting up a trauma institute in Detroit, was offered a position as a chair at UCD in May 1997. He served as chair of the safety

---

102 Dr. Meyers was unclear about the date of this meeting. However, he said he had this discussion with Dr. Muizelaar and then did not hear anything more about the procedure until later, after Patient 3 received the procedure. The evidence suggests that this meeting took place in late 2010 or early 2011, during the period when Dr. Muizelaar was enthusiastic about the progress of Patient 2.
and monitoring boards of the NIH and on a number of panels for the VA regarding treatment of head injury and stroke.

Dr. Muizelaar heard several stories of patients with glioblastoma experiencing wound infection following surgery surviving much longer than anticipated. He noted that he had one patient in the VA who got an infection during surgery and then survived an additional 15 years. At UCD, he had a patient who experienced a wound infection when operated on in Japan, and survived an additional 20 years. Dr. Muizelaar hired Dr. Schrot as a resident and kept him to assist treatment of brain tumors. At this time, Dr. Muizelaar discussed establishing animal studies for intentional infection with Dr. Schrot, however, Dr. Muizelaar was very busy clinically and there was insufficient funding to support the research.

In 2008, Dr. Muizelaar was approached by regarding treatment of a glioblastoma patient. Dr. Muizelaar had a lengthy discussion with the patient’s and determined that wound infection was likely the only hope for survival. Dr. Muizelaar charged Dr. Schrot with seeking approval for the surgery. Dr. Muizelaar stated that the Bioethics Committee was convened to review the treatment, and Dr. Kon was the chair of that committee. Dr. Muizelaar stated that the committee did not object to the treatment and provided approval contingent upon IRB approval. Dr. Muizelaar stated that if the committee found the treatment unethical, he would not have pursued any further approval and would have abandoned the treatment. Dr. Muizelaar noted that this committee was convened primarily because the patient , and that innovative treatment is often conducted without review. Dr. Muizelaar did not recall any discussions with Dr. Asmuth or Dr. Anderson regarding the treatment but knew that Dr. Schrot was directed to contact the FDA. Dr. Muizelaar believed that FDA approval was required because the bacteria needed to be ordered at that time. Dr. Muizelaar defined innovative treatment as any treatment for which the efficacy has not yet been proven. He stated that often innovative treatment occurs first and is then followed by a clinical trial to prove efficacy. Dr. Muizelaar used his work in treating heavily ventilated brain injury patients in Richmond as an example.

Dr. Muizelaar has conducted numerous clinical trials and stated that he has significant experience with the IRB and review procedures. Dr. Muizelaar stated that there is a difference between experimental protocol and innovative treatment. Dr. Muizelaar believed the intentional wound infection was innovative treatment, and therefore, did not require IRB approval. Dr. Muizelaar stated that the bacteria used for the treatment had been growing in the laboratory since 2009. He stated that Dr. Schrot found more research supporting the treatment and started the lab. Dr. Muizelaar stated that bacteria can be obtained anywhere, but they ordered this bacteria because they wanted a controlled strain. Dr. Muizelaar stated that bacteria transitions to “local” status within ten generations, but such measurement is more dependent upon the local lab technician’s experience with the bacteria. Dr. Muizelaar was unaware of any FDA regulations concerning the origination/designation of bacteria. Dr. Muizelaar stated that the FDA may approve the use of bacteria for human use if you have data support, but that he did not want to do
CONFIDENTIAL

a study and instead wanted to treat a single subject. Dr. Muizelaar did not receive any further correspondence from the FDA.

Dr. Muizelaar stated that animal studies for the treatment occurred from 2008 to 2009. Dr. Muizelaar was not directly involved in the studies but provided that the primary purpose was to gather data showing wound infection would cause treated rats to live longer. Dr. Muizelaar did attend conferences where Dr. Schrot presented data from the studies.

Patient 1 was [REDACTED]. After treatment at [REDACTED], the patient was discharged with a prognosis of 2-3 months to live. Dr. Muizelaar had discussed wound infection treatment with the patient previously and revisited the discussion after this discharge. Dr. Muizelaar did not believe they needed to convene an ethical committee as the patient could give consent, however, he thought they needed guidance from the IRB and charged Dr. Schrot with contacting the IRB. Dr. Muizelaar did not believe IRB or FDA approval would be necessary as they were treating a patient and not conducting research. Dr. Muizelaar did not speak with Eric Mah prior to treatment. Dr. Muizelaar did speak with CMO Dr. Siefkin who informed him to obtain good informed consent. Dr. Muizelaar did not review the email from Dr. Siefkin prior to surgery but stated that he did complete all tasks outlined by Dr. Siefkin, including speaking with the hospital director, Ann Madden Rice, about the cost. Dr. Muizelaar and Dr. Schrot prepared the consent form together and reviewed it with several family members present.

Treatment of Patient 1 with intentional wound infection occurred on [REDACTED] 2010. Dr. Muizelaar stated that the operating room was briefed on the procedure and that technicians dealt with the bacteria when the procedure was finished. Dr. Muizelaar acknowledged that some OR protocols were not followed, which were subject of the Medicare investigation, but that Dr. Muizelaar and Dr. Schrot were not in charge of the OR and were found not at fault. The patient survived for an additional eight weeks after surgery. Dr. Muizelaar did not believe the bacteria implant caused any harm.

Patient 2 was a patient of Dr. Muizelaar who experienced recurrence of a tumor following surgery. Dr. Muizelaar discussed intentional wound infection treatment with the patient and [REDACTED] and decided that it was [REDACTED] only hope. Dr. Muizelaar discussed the treatment with Dr. Fred Meyers at a reception honoring faculty members. Dr. Muizelaar stated the Dr. Meyers instructed him to do his due diligence and get good consent forms. Dr. Muizelaar stated that he did not remember Dr. Meyers telling him to seek IRB approval, but that the doctors did revisit the IRB even though he “didn’t know why.” Dr. Muizelaar recalls seeing Eric Mah’s [REDACTED] email but does not remember discussing with Dr. Siefkin. He also recognized that they would need animal data to apply for an IND but they did not intend on treating additional patients.

Dr. Muizelaar stated that research would undoubtedly require IRB approval, but the doctors were not conducting research. Dr. Muizelaar stated that there was no completed animal research prior to treatment of Patient 2 to seek an IND, but that as the procedure was innovative
treatment, it only required review by medical staff. Dr. Muizelaar stated that there should be a clear line between innovative treatment and research. He defined research as testing a hypothesis to draw conclusions, whereas treatment is only about enhancing results for the individual patient.

Dr. Muizelaar learned about Patient 3 after they came into the ER; they received an MRI which showed a large tumor. Dr. Muizelaar said he informed them about the potential intentional wound procedure as well as conventional treatment options. He said that he told them that if they proceeded with this unconventional method, they would not qualify for other trials, including a clinical trial at UCSF. He confirmed that he did not discuss the procedure with anyone else at UCD, including Dr. Siefkin or the IRB; he noted that it was patient treatment. He conducted the procedure on Patient 3 a few days after they had come into the ER and was diagnosed with glioblastoma.

While Patient 3 was still alive and “improving,” the Ad Hoc Ethics Committee was discussed to consider the treatment of potential future patients. Dr. Muizelaar stated that Dr. Meyers recommended the committee after Dr. Muizelaar was approached by another patient about treatment who was a future patient. This new patient would likely be okay without treatment for six to nine months, so Dr. Muizelaar felt that he was a “future” patient for whom they should seek IRB approval. Patient 3 died.

In reviewing the cease and desist letter from Dr. Siefkin, Dr. Muizelaar stated that he could not remember Dr. Siefkin instructing him to contact the IRB, but that, in any event, they did. Dr. Muizelaar believed they had clear approval from Eric Mah in his emails. He stated that he did not discuss treatment of Patient 3 with anyone because they was diagnosed as a patient in the ER and it was unusual circumstances. Dr. Muizelaar believed the IRB had confirmed that the treatment was not research twice, and they treated the third patient under such belief. He stated that they revisited the IRB for potential patient 4 when they believed the treatment was moving to research. Specifically, he stated that “later” in 2011 they were more likely to do a research project, which is why they decided to proceed with the Ad Hoc Ethics Committee and involve the IRB.

Dr. Muizelaar stated that Dr. Schrot prepared the Prospectus in the file, which was prepared for the Ad Hoc Ethics Committee, the IRB, and potentially the FDA. He also stated that the Record of Invention was only prepared and submitted when the patient of one of the his patients suggested that he submit it. Dr. Muizelaar did not believe the procedure was patentable, and stated that they received a refusal of the patent before Patient 3, within a week of submission of the ROI. The consent form for Patient 3, unlike the forms for Patients 1 and 2, 103

103 As discussed below, the Technology Transfer Office has no evidence suggesting that there was ever a denial or refusal of a patent. Dr. Muizelaar stated in his interview that he would provide materials to demonstrate the refusal, but he was not able to locate any such documents.
allowed for publishing of data related to the procedure. Dr. Muizelaar was unsure why this was added and noted that you can request consent for publication in retrospect.

H. Interview of Dr. Robert O’Donnell

Dr. O’Donnell has been a Professor of internal medicine for 25 years. He has an emphasis on oncology, and hematology, and regularly sees brain tumor patients. He sits on the tumor board every other week. In addition, he has a clinic with Dr. Schrot. For the past year, Dr. O’Donnell has served on the IRB; he was also on the VA Medical Center’s IRB for seven years.

He said that he has heard Dr. Muizelaar and Dr. Schrot discuss the concept of the procedure for treating glioblastoma patients with bacteria to create an infection for the past five years. He first learned about the procedure that was performed on Patient 1 when Dr. Schrot called him at the VA Medical Center to ask him questions about growth factors. When he asked Dr. Schrot why he needed the answer, Dr. Schrot told him that he had used the procedure on a patient. When Dr. O’Donnell asked if Dr. Schrot had obtained approval, he said that he did get approval from the IRB.

Dr. Schrot had called him because after they had put the bacteria in the glioblastoma patient’s brain, the white cell count was going down. He asked Dr. O’Donnell for advice on how to increase the white blood cell count. Dr. Schrot asked Dr. O’Donnell if they should give the patient Erythropoietin (“EPO”). Dr. O’Donnell was confused by the request since EPO is not used for white blood cell elevation. He asked Dr. Schrot about the bacteria; it was grown in the lab so Dr. Schrot would know its sensitivities and could give the patient a antibiotics to kill bacteria.

Around this time, Dr. Ted Wun (the Hematology/Oncology Chief) approached him to ask about the procedures and voice concern. Dr. Wun asked Dr. O’Donnell if Dr. Schrot and Dr. Muizelaar had approval, and Dr. O’Donnell told him that he understood they had approval from the IRB. Dr. Wun was in disbelief. Dr. O’Donnell again asked Dr. Schrot about the approval and was told that they had the approval of the IRB and the CMO, Dr. Siefkin, had also approved.

Later, likely after Patient 2 was treated, Dr. Schrot showed him the patient’s MRI. Dr. Schrot was happy about the results. Dr. O’Donnell does not recall any other clinical discussions about the other patients. Other than the questions regarding white blood count, Dr. O’Donnell was never consulted about treatment.

On another occasion, Dr. O’Donnell asked Dr. Schrot if they had hospital approval. He said they did because it was “innovative use” for a novel medication, not an experiment. Dr. O’Donnell informed us that he has not heard the term “innovative use” before. He was familiar with the term “compassionate use” but did not understand how something would be considered “innovative.” He again noted that he had the impression from Dr. Schrot that Dr. Schrot believed that everything was approved.
At some point after another patient, Dr. Schrot told Dr. O’Donnell about the application for a patent. Dr. O’Donnell asked him what data they would use because they could not use compassionate use data. He does not recall getting an answer. He also asked Dr. Schrot about FDA approval; Dr. Schrot stated that the FDA did not care because bacteria did not cross state lines. Dr. O’Donnell said that Dr. Schrot seemed genuine at the time and his answers seemed truthful.

He also asked Dr. Schrot at one time: “Who pays for all this?” Dr. Schrot told him that there was nothing to pay for. Dr. O’Donnell also inquired about the process for sterilizing the OR; Dr. Schrot told him that of course the OR gets sterilized after the procedures.

The issue later came to the attention of the IRB in the Spring of 2011. Although Dr. O’Donnell was on the IRB at that time, he did not discuss the procedure or the patients as part of his IRB committee, but he was presented with other committee’s review and opinion of the procedures. He said that John Keltner on the IRB committee recommended that the IRB write a formal cease and desist letter to make sure it did not happen again. Dr. O’Donnell noted that Dr. Schrot seemed unfazed after the media reports came out; Dr. Schrot seemed stoic. He again said that Dr. Schrot did not give him the impression that he was lying, but he might be in denial.

At the time it was occurring, Dr. Schrot really wanted to talk about the patients getting better: he did not share much other information. The only time he (Dr. Schrot) was really enthusiastic was after Patient 2 when [redacted] was improving. Dr. O’Donnell opined that he thought Dr. Schrot and Dr. Muizelaar knew that they were not supposed to do the procedure. But the only time they got a definitive “no” was after Patient 3 when the IRB sent the cease and desist letter.

It was noted that Dr. O’Donnell was listed as a member of the Ad Hoc Ethics Committee. He said that after Patient 3, Dr. Schrot told him they wanted to do more so they were putting together this committee. Dr. O’Donnell recommended an infectious disease doctor for the Ad Hoc Ethics Committee. He did not discuss the Committee with anyone and there was never a meeting of the Committee. He believes that the Committee was formed to help reverse the decision that they could not proceed. He said the Committee never approved the Prospectus and that he would not have voted to approve it.

He also noted that he offered to assist Dr. Schrot with the development of a protocol at some point, but this did not happen. He said that when he first heard of the procedure on Patient 1, he assumed that a protocol was in place. Had he been consulted, he would have made other suggestions for the proposed treatment, such as autoclaving. But he was not consulted and did not have discussions with anyone about the rat study.

When asked about the issue regarding the origination of the bacteria, Dr. O’Donnell said from a regulatory standpoint, this should be a nonissue. The answer from the IRB should have been “no” regardless of where the bacteria came from. In any event, his understanding is that if
Dr. Schrot had gathered the bacteria from the environment, it would have been his or local. If he bought it, even when cultured, it would not be a local

Dr. O’Donnell was never asked to opine on the consent forms. He does draft consent forms when he is working on a protocol for his own projects and said that it is important to ensure that the forms are understandable. He did not think Dr. Schrot was anticipating any financial gain from the procedure, despite the patent application.

He said again that he did not think the surgeons got a clear “no” from IRB until the cease and desist letter was issued. He said that telling a neurosurgeon that “I wouldn’t do that if I were you” does not mean “no.” But he said they had a duty to make sure they had permission. There seemed to be some “gaming” of the system on their part.

I. Interview of Dr. Claire Pomeroy

Dr. Claire Pomeroy is the Chief Executive Officer of UCD Health System, the Vice Chancellor for Human Health Sciences and the Dean of the UCD School of Medicine. We included Dr. Pomeroy in our interviews because her name was referenced in the March 21, 2011 email from Dr. Muizelaar to Dr. Siefkin in which Dr. Muizelaar wrote that “both cases 2 and 3 were discussed with deans Meyers and/or Pomeroy.”

Dr. Pomeroy stated that the characterization that she “discussed,” the cases with Dr. Muizelaar is not accurate. She said that on two occasions she recalls Dr. Muizelaar mentioning that he was doing these cases in passing. It was “just a mention.” They never had a formal meeting or discussed the cases.

When we asked her whether Dr. Muizelaar had discussed the approval process for these cases with her, she said that he did not. She said that she speaks with Dr. Muizelaar on a regular basis, just like she speaks to the other doctors. She noted that she heard from the IRB in 2011 when it was conducting its investigation but that the IRB only notified her because of the potential surgical room violation. Per IRB’s suggestion, she shared the information from the IRB with the Chief Compliance Officer, but she was otherwise careful to maintain confidentiality.

J. Interview of Teresa Porter

Teresa Porter is the Chief Compliance Officer for the U.C. Davis Health System. Her primary focuses are ensuring compliance with privacy, conflict of interest, and billing regulations, including research billing activity. Ms. Porter has worked with the Compliance Program since 1996 and previously conducted investigations, which she now oversees. Ms. Porter did not oversee the investigation of Dr. Muizelaar and Dr. Schrot, but provided staffing for the investigation from her office. In the past, Ms. Porter had monthly meetings with the IRB, the CTSC (which no longer exists), and the Office of Research Compliance to be sure the various entities were not duplicating compliance efforts.
CONFIDENTIAL

Eric Mah first notified Ms. Porter by telephone in [redacted] of 2011 that Dr. Muizelaar and Dr. Schrot had treated three glioblastoma patients with intentional wound infection. Ms. Porter was not previously consulted by the doctors regarding the treatment. Ms. Porter stated that if she had been consulted regarding the innovative treatment, she would have referred the doctors to the IRB and the Chief Medical Officer. Ms. Porter then contacted Rachel Nosowsky to ensure that proper procedures were followed for the investigation, and appointed Gina Holleman to conduct the investigation. Thereafter, Ms. Porter was not involved in the investigation and did not provide any opinions for any resulting report.

K. Interview of Dr. Rudolph Schrot

Dr. Rudolph Schrot was selected for a residency position and started work at U.C. Davis in 1999 with Dr. Muizelaar. Dr. Schrot first worked as an intern and completed his postgraduate medical training in 2004. He was then recruited to join the faculty, beginning as an assistant. In 2011, Dr. Schrot was promoted to associate professor, his current position. Dr. Schrot practices general neurosurgery, with an emphasis in sacrococcygeal disorders.

Dr. Schrot noted that anecdotal evidence existed for the wound infection procedure for treatment of malignant brain cancer since the 1900s. Dr. Schrot stated that Dr. Muizelaar suggested intentional infection based on his observations of accidental infections in his patients and the previous literature. Dr. Schrot provided that the intentional wound infection procedures were performed on Dr. Muizelaar’s patients and that Dr. Schrot was not the attending physician, although he participated in the care.

Dr. Schrot discussed the 2008 [redacted] patient, stating that the patient’s [redacted] talked to Dr. Muizelaar about the wound infection procedure, and Dr. Muizelaar approached Dr. Schrot about exploring the option. Dr. Schrot then contacted the Bioethics Committee chaired by Dr. Kon and arranged for the consultation. The result of the Committee vote was approval of the procedure dependent upon IRB approval. This was the first time that Dr. Schrot had pursued approval for any innovative procedure. Dr. Schrot could not remember precisely why he approached the Bioethics Committee at that time, but it seemed appropriate, [redacted]. Dr. Schrot saw the Committee’s direction to seek IRB approval as “a due diligence measure.”

When asked about communications with the FDA, Dr. Schrot provided that he prepared a protocol for IRB review after determining that he would need to pursue a single patient treatment IND, which requires both FDA and IRB approval, since there was no locally available product. Dr. Schrot provided that he primarily spoke with Dr. Anderson at this time. Dr. Schrot did view the 2008 proposed procedure as a gray area regarding approval and decided to fill out a full committee application to the IRB. In discussing subsequent communications from Dr. Anderson, Dr. Schrot stated that he understood Dr. Anderson to be recognizing the urgency of treatment for the [redacted] patient, thus allowing treatment with expedited IRB approval if the FDA approved the procedure but requiring full IRB approval for treatment of any future patients.
CONFIDENTIAL

Dr. Schrot stated that he understood from Dr. Skip Nelson that FDA approval would not have been required if he were able to obtain the bacteria locally.

Dr. Schrot defined innovative care as treatment of a single patient using a non-standard method of treatment, specifically referencing use of a drug in an off-label manner. He further provided that innovative care is intended to benefit the patient, whereas an investigational study is pursued to produce generalizable knowledge and not treat the patient. Dr. Schrot stated that the absence of animal data does not determine whether a procedure is innovative care versus investigational treatment or research. Dr. Schrot did not recall researching such definitions with the FDA but felt that innovative care was not research and was outside the purview of the FDA. At the time, Dr. Schrot did not look for any locally available bacteria because he did not believe there was one. Dr. Schrot did not pursue the 50.54 panel review and abandoned the efforts to treat the [REDACTED] patient with intentional wound infection.

Dr. Schrot pursued the grant proposal for animal studies after recognizing the “knowledge gap” and lack of “any appropriate preclinical studies.” The grant was not funded. Dr. Schrot worked with Lorena Navarro, an assistant professor of microbiology, to order bacteria for the animal studies. He knew that the bacteria was ordered but did not review the Materials Transfer Agreement from the ATCC at the time.

Dr. Schrot was told about Patient 1 in [REDACTED] 2010. Dr. Muizelaar asked Dr. Schrot to investigate whether it would be possible to treat Patient 1 with intentional wound infection. Dr. Schrot told Dr. Muizelaar that he doubted they could obtain approval as they did not yet have the adequate data to make an IND application, but Dr. Muizelaar told him to contact the IRB. Dr. Schrot stated that he contacted Mr. Mah and told him about the 2008 attempt to obtain approval and the issues encountered. Dr. Schrot also believed the 2008 process was documented in the IRB investigation findings. Dr. Schrot did not approach Dr. Asmuth or Dr. Anderson in 2010. Mr. Mah indicated that the treatment of a single patient with the now locally available bacteria, as represented by Dr. Schrot, did not require FDA authority.

Dr. Schrot said that he related Eric Mah’s direction to talk with Dr. Siefkin, the hospital CMO, to Dr. Muizelaar. Dr. Muizelaar assumed the responsibility of talking to Dr. Siefkin and any other hospital official; Dr. Schrot did not speak with Dr. Siefkin. Dr. Schrot did not see the [REDACTED] 2010 email from Dr. Siefkin until after the Patient 1 was [REDACTED]. He discussed the email with Dr. Muizelaar in the operating room. In reviewing the email from Dr. Siefkin, Dr. Muizelaar stated that the issues had all been addressed. Dr. Muizelaar represented that the Bioethics Committee determination from 2008 satisfied that concern, and that he had addressed costs with hospital administration, who were aware of the innovated treatment. Dr. Schrot was not present for the entire procedure.

To facilitate transport of the bacteria to the operating room, Dr. Schrot first discussed the treatment with Dr. Navarro. Dr. Schrot directed graduate student [REDACTED] to prepare the bacteria cultures for the procedure. The bacteria was housed in three containers for transport to the hospital and then into the operating room. [REDACTED] was driven to the hospital, and the
bacteria was taken straight to the operating room. Dr. Schrot stated that everyone in the operating room was aware that they were conducting an innovative procedure to create a wound infection using the bacteria. Dr. Schrot believed that the transport of the bacteria was in accordance with standard laboratory safety procedures and was not aware of additional procedures at the time. He understands there to be different requirements now.

Dr. Muizelaar later approached Dr. Schrot about Patient 2. Dr. Schrot stated that he had a lengthy call with Eric Mah, who told him if this was a single patient, it was innovative care and not research. Dr. Schrot stated that Mr. Mah stated if they were to set out a program to treat multiple patients, it would become research and they would need IRB approval. Dr. Schrot interpreted Mr. Mah’s confirmation email as recommending IRB approval after treatment of a third patient, not for a third patient. Dr. Schrot stated that Mr. Mah’s email contained “recommendations,” not directives. Dr. Schrot also stated that he found the language of “anticipating another future patient” to be unclear.

Dr. Schrot said that did not know whether Dr. Muizelaar spoke with Dr. Siefkin prior to treatment of Patient 2. Dr. Schrot believed that later emails discussing pursuit of IRB approval was only relevant to establishing a pilot study. Dr. Schrot provided that he used the phrase “cautious clearance” to describe Mr. Mah’s caution that treatment of multiple patients could be seen as research requiring an IND. Dr. Schrot also stated that he was concerned that the bacteria was being prepared quickly enough for the procedures and that he wanted to see research progress independent of treatment of the patients. The procedure for Patient 2 was similar to that for Patient 1, in that Dr. Muizelaar was the surgeon and Dr. Schrot coordinated culturing and transport of the bacteria.

When asked whether he gave presentations about the procedure, Dr. Schrot reviewed his notes and stated that he gave some informal talks regarding Patients 1 and 2 at tumor board, but he did not recall giving presentations.

Dr. Muizelaar again approached Dr. Schrot about Patient 3. Dr. Schrot did not specifically remember being consulted as to his opinion as to whether the treatment was advisable, but stated that he did raise the previous discussion with Eric Mah regarding treatment of future patients. Dr. Schrot noted that Patient 2 was experiencing dramatic regression of tumor at this time, and he felt that Patient 3 should be aware of all the options. Dr. Schrot was also the principal investigator for another trial at this time offering drug treatment and felt he should inform the patient of that. Dr. Muizelaar was already going to take the patient into surgery for resectioning, so the patient had to decide whether to proceed with the wound infection at that time. Dr. Schrot stated that it was Dr. Muizelaar’s judgment that the patient needed to undergo surgery soon, and additional discussions with the IRB weren’t necessary. Dr. Schrot was not aware of any additional discussions regarding Patient 3 with Dr. Siefkin.

Dr. Schrot did not believe that Eric Mah had authority to address patient care in the hospital, or the IRB authority to direct patient care. Dr. Schrot stated that he posed similar questions at recent training and was told that the FDA does not regulate innovative care.
Dr. Schrot stated that he prepared and drafted the consent forms for all three patients. Dr. Schrot confirmed that no ethics committee was convened to specifically address treatment of the three patients. Dr. Schrot stated that he submitted the record of invention because he thought it might be something the University was interested in and he was required to do so because of his contract. He stated that he was told the idea was ultimately not patentable, but he didn’t recall receiving confirmation of this or rejection of the ROI in writing.

Dr. Schrot was approached by Dr. Muizelaar about potential Patient 4 in [redacted] 2011, and the patient was referred to Dr. Schrot by [redacted]. Dr. Schrot and Dr. Muizelaar met with the patient and [redacted] family to discuss the treatment. Dr. Muizelaar felt that his patient did not need immediate treatment and was a “future patient.” Dr. Muizelaar told Dr. Schrot that Dr. Meyers had recommended an ad hoc ethics committee regarding treatment of the fourth patient, as the doctors were concerned that they could not timely obtain IRB approval. Dr. Schrot never spoke with Dr. Meyers directly about the committee. Dr. Schrot prepared the prospectus and set up a meeting with Eric Mah to review. Mr. Mah stated that he was unaware of treatment of the third patient. Dr. Schrot then met with Mr. Mah, Dr. Asmuth, Dr. Muizelaar, and Karen Smith on [redacted]. Either during or just before the meeting, Patient 3’s condition began to deteriorate. At the meeting, Dr. Schrot and Dr. Muizelaar were told not to treat any additional patients without a clinical trial and IND, which would require preclinical work. Dr. Schrot viewed the subsequent cease and desist email as confirmation of what was discussed at the meeting where the doctors had agreed not to treat future patients. The only meeting Dr. Schrot attended with Dr. Siefkin was the peer review in [redacted] 2011.

Dr. Schrot believes that he was seeking IRB approval throughout the treatment of the patients but that the rules changed midstream. He believes the area is still gray but, in light of his experience, will view IRB recommendations and guidance as directives. He also believes the recent innovative care policy comports with his understanding that individualized treatment of patients is not research.

I. Interview of Dr. Allan Siefkin

Dr. Siefkin has been the Chief Medical Officer (“CMO”) since 1993. He has worked at UCD since 1975 and has been a member of the faculty since 1981. As the CMO, he is responsible for physicians’ practices in hospital and clinic and reports to hospital CEO. He explained that the Chancellor for Human Health Affairs (the actual title is “Vice Chancellor for Human Health Sciences”)—also now the Dean—is the governing body of the hospital and is responsible for peer review functions.

Dr. Siefkin then asserted California Evidence Code section 1156, 1157 protections for the information he was about to provide. He stated that he first heard about the proposed treatment of glioblastoma patients was sometime in 2008 or 2009 when Dr. Muizelaar spoke to him about a [redacted] patient. Dr. Muizelaar showed him some literature. He was aware that the case went to the Ethics Committee but ultimately the care was not provided to [redacted].
On [redacted] 2010, Dr. Muizelaar spoke with him after a counsel chairs meeting about Patient 1. Dr. Muizelaar told him that Dr. Schrot spoke with the IRB chair and said that he was instructed to perform the procedure as compassionate care. Dr. Siefkin spoke with Dr. Muizelaar extensively about informed consent. He reviewed the consent form and gave Dr. Muizelaar and Dr. Schrot changes to include.

He sent an email to Dr. Muizelaar on the same day of the procedure that discussed complications of treatment, further IRB approval, and costs of cases. He directed Dr. Muizelaar to Jim Goodnight for continuing procedures.

He explained that on [redacted], John Grubbs, pharmacy director, stopped him in the halls to discuss a letter from a pharmacist regarding her concern about Patient 3. The emails that had been sent to Dr. Siefkin that went to his trash instead of his inbox, so he was unaware of them until he was approached by Mr. Grubbs. Dr. Siefkin immediately investigated the three patients and ultimately wrote a cease and desist letter to Dr. Muizelaar.

Dr. Siefkin said that he thought the Ad Hoc Ethics Committee had met and that they issued a determination, based on an email from Karen Smith. Dr. Siefkin said that there is a formal hospital ethics committee that he would have used but Dr. Muizelaar says that Dr. Fred Meyers told him to form the Ad Hoc Committee. He believed that the Ad Hoc Ethics Committee that was formed was well rounded; there were no apparent conflicts.

Dr. Siefkin asked Dr. Muizelaar and Dr. Schrot to come to peer review committee. He explained that there are three levels of review. [Redacted up to this point].

Dr. Siefkin said that he believed Dr. Muizelaar and Dr. Schrot had good intentions and that they believed they had permission from CMO and IRB—he did not believe they were being dishonest. He confirmed that he went to Dr. Muizelaar’s home to discuss Patient 3 with him; he was unhappy that Dr. Muizelaar had proceeded. He noted that he went to Dr. Muizelaar’s home because he was not in the office [redacted].

He added that Dr. Schrot and Dr. Muizelaar are long standing members of the medical staff and have some very fine characteristics. They are neurosurgeons with very difficult practices. Dr. Muizelaar is “transparent to a fault.” Dr. Schrot was trained by Dr. Muizelaar; he was working with and under the principle direction of Dr. Muizelaar but is not considered an “underling.” Dr. Siefkin stated that they truly believed in the promise of this treatment.
CONFIDENTIAL

M. Interview of Karen Smith, R.N.

Karen Smith is a retired nurse who is the facilitator of a brain tumor support group. Ms. Smith has worked at UCD off and on since 1975. In 1983, she worked on a national spinal cord injury study at UCD, which continued until the mid-1990s. She subsequently became involved with a small brain tumor study. Immediately before her retirement in 2006, she worked in the Department of Neurosurgery. She continues to work in that department on a part-time basis (two days a week). She worked with Dr. Muizelaar from 2008-2011, assisting with an angioplasty study and then a traumatic brain injury study. She did not work in surgery in that time frame.

Ms. Smith has facilitated the brain tumor support group since around 1990. She has known many patients with glioblastoma through the support group. The group is a community group, open to patients from different hospitals of different doctors throughout the community. She then discussed some of the experiences that she has had with brain tumor patients over the years.

Ms. Smith first heard about the proposed procedure around the time that Dr. Schrot was seeking approval for the patient in 2008. She recalls that Dr. Schrot sought approval and it was denied. She could not recall any specific conversations but she believed that the procedure had been denied at that time because the patient had

She does not work in the laboratory and did not know if the rat study was ever proposed or presented. She said she had no role in setting up any studies of that nature.

Ms. Smith recalled that Patient 1 had “asked for the innovative therapy.” She recalled being present when Dr. Muizelaar talked to the family about consent. Patient 1’s was present during the consent form discussion. Ms. Smith had no role in preparing the consent form, although she did read it. She never discussed the approval process regarding the procedure with anyone.

Ms. Smith did not see Patient 1 again until after the procedure had been conducted and was in recovery. She said that “stayed stable for a long period of time.”

Around 2011, Dr. Muizelaar asked Ms. Smith to Chair an Ad Hoc Ethics Committee. He asked her to put the committee together. She said at this time Patient 1 had died, Patient 2 was alive and doing well, and Patient 3 was in the intensive care unit. Dr. Muizelaar told her that the purpose of the committee was to review a proposal from Dr. Muizelaar and Dr. Schrot to do the “innovative treatment with the bacteria” on 4 or 5 more glioblastoma patients. noted that there was another patient already requesting the treatment.
She received a Prospectus that she said was written by Dr. Schrot. The individuals that Ms. Smith selected for the Ad Hoc Ethics Committee were: Dr. Bob O’Donnell (because of his role as an oncologist); Dr. Stu Cohen (because of his expertise with infectious diseases); and Dr. Prasad (because he did his residency with UCD and she knew him professionally and personally, and because he is involved in neurosurgery and has served on a bioethics advisory board).

Ms. Smith said that she was aware at this time that there was caution regarding administrative approval, which she called a “misunderstanding.” She said she did not think that was the reason Dr. Muizelaar asked her to form the committee. She said she thought it was because of his desire to do the procedure on more patients and he knew that she had a longstanding interest in brain tumors and that she was familiar with the faculty.

Ms. Smith was then showed the email from her dated [redacted] 2011, in which she sent the Prospectus to the proposed members of the ad hoc committee and which said that the committee was formed at the behest of Dr. Fred Meyers. Ms. Smith said she never discussed this with Dr. Meyers.

Ms. Smith was also showed an email dated [redacted] 2011, which she authored that stated: “We have reviewed the Prospectus developed by Rudolph J. Schrot, MD, MAS and J. Paul Muizelaar, MD, PhD and believe it to be a reasonable treatment for glioblastoma. We would recommend continuing this informal clinical activity to include an additional 5-6 patients with the understanding that an IRB-approved formal protocol be developed as soon as possible.” 104 Ms. Smith said she did not receive any comments in response to the email. Ms. Smith confirmed that there was never a meeting of the proposed Ad Hoc Ethics Committee and thus, never approval by the Ad Hoc Committee.

On [redacted] 2011, she spoke with Eric Mah about the proposed Ad Hoc Ethics Committee and the Prospectus. At that time, they discussed setting up a meeting with the committee, Dr. Muizelaar, Dr. Schrot, Mr. Mah and the IRB Chairs (Dr. Anderson and Dr. Asmuth). When she later spoke with Dr. Schrot about the meeting, Dr. Schrot said that if he had a choice between IRB Chairs, he preferred Dr. Anderson because he was a surgeon. She told Mr. Mah of Dr. Schrot’s preference.

The meeting took place on [redacted], 2011; Ms. Smith, Mr. Mah, Dr. Asmuth, Dr. Muizelaar and Dr. Schrot attended. The other three proposed members of the Ad Hoc Ethics Committee did not attend the meeting. She said Dr. Muizelaar was the last to arrive. When he came in he said, “I’ve got mud on my face because our 3rd patient is not doing well. She is

104 Smith email to Mah, Robert O’Donnell, Stuart Cohen, Praveen Prasad, copying Dr. Schrot and Dr. Muizelaar, dated [redacted], 2011.
going to die.”\textsuperscript{105} She did not recall much else being said at the meeting and said that Dr. Asmuth was working on his computer and did not say much. Ms. Smith recalled that they did not discuss much at the meeting because that had learned of Patient 3’s condition. Ms. Smith said things were “let go at that time,” and they did not discuss the other patients.

Ms. Smith said that she was shocked when Patient 3 died. She said that nothing else was done regarding the Ad Hoc Ethics Committee.

Ms. Smith said that she has worked for Dr. Muizelaar and Dr. Schrot for many years and both are honest physicians. She said she did not believe this was a deliberate act of defiance. She said she thinks Dr. Muizelaar and Dr. Schrot felt they had permission to do the procedure on the patients. She said she feels bad that this has happened to UCD and noted something similar happened in the 1980s with another Sacramento Bee reporter.

On August 3, 2012, she received an email that Dr. Muizelaar sent to everyone in the Neurosurgery Department, after the first article in the Sacramento Bee, which discussed his view on what had happened.

She again communicated her belief that Dr. Muizelaar and Dr. Schrot had good intentions.

N. Summary of Evidence Concerning Record of Invention

On 2011, Dr. Muizelaar and Dr. Schrot signed and submitted to UCD Technology Transfer Services (“TTS”) an ROI through InnovationAccess/TTS for the intentional surgical wound infection procedure, Exhibit 130. The ROI states, among other things,“[p]urified cultures of Enterobacter aerogenes are obtained from ATCC and allowed to grow overnight in Luria broth at 37°C. The treatment is applied during a craniotomy surgery for recurrent glioblastoma.” The ROI was submitted after the procedure had been conducted on Patients 1 and 2, but before Patient 3 had ever met with Dr. Muizelaar or Dr. Schrot.

TTS assigned UC Case No. 2011-495-1 to the ROI for tracking purposes. The case was originally assigned to Intellectual Property Officer Randi Jenkins but for non-case related reasons was reassigned to Raj Gururajan.

On 2011, after the procedure had been performed on Patient 3, Randi Jenkins and Raj Gururajan met with both inventors to discuss the invention. Mr. Gururajan recalls that they discussed: (1) the invention; (2) the ethics of patenting medical procedures (which is contrary to the AMA’s position) and (3) the possibility of Dr. Muizelaar and Dr. Schrot creating composition of matter with respect to specific bacterial cultures in the future could be possibly

\textsuperscript{105} Ms. Smith said Dr. Muizelaar either said that he had “mud on my face” or “egg on my face” but she was not sure which one.
be patentable subject matter, depending on what the inventors would invent. No determination regarding the ROI was made or communicated at the [redacted] 2011 meeting.

After the meeting, on May 5, 2011, Mr. Gururajan became aware of an investigation related to this procedure when he received an email from Gina Guillaume-Holleman and Rachel Nosowsky, UC Office of General Counsel, requesting an interview to discuss the ROI. Because of the investigation, TTS decided not to have any further communications with Dr. Muizelaar and Dr. Schrot regarding the ROI. The meeting on [redacted] 2011, was the last time that TTS communicated with Dr. Muizelaar and Dr. Schrot regarding the ROI.

TTS ultimately decided not to file a patent application regarding Dr. Muizelaar and Dr. Schrot’s ROI. There were two main reasons for this decision. First, as noted above, the AMA had adopted a position that it is unethical to patent inventions that are solely medical procedures. In accordance with that position, UCD does not file patent applications on inventions that are strictly medical procedures (although it does file applications for inventions claiming medical devices and therapeutics). Second, TTS determined that the ROI did not have an “adequate description of a novel composition of matter related to bacteria to provide a basis for IA to consider filing a patent application claiming a therapeutic.” The ROI is currently listed in the UC Patent Tracking System as “in abeyance,” which means it is suspended. The case can be kept in abeyance indefinitely, closed, or reactivated depending on circumstances.

TTS also noted that Gina Guillaume-Holleman asked whether InnovationAccess/TTS negotiated a Material Transfer Agreement in 2009 between UCD and ATCC for an *enterobacter* culture from ATCC for Dr. Muizelaar and Dr. Schrot. TTS stated that it searched its database for MTAs and have found no record of InnovationAccess/TTS ever executing an MTA with ATCC for either Dr. Muizelaar or Dr. Schrot. It did locate one record of an MTA for Dr. Schrot, dated May 28, 2009, for receipt of rat astrocytoma cells from Dartmouth to be used in creating a rat glioblastoma model.

### O. CMS Report

The CDPH, the California Medicare survey agency, conducted a survey at UCD Medical Center on August 30, 2012. It noted a number of deficiencies in its report, referred to herein as the CMS Report. UCD Medical Center CMO, Dr. Siefkin, responded to the alleged deficiencies. Among other points, Dr. Siefkin noted:

> While we agree that the surgeons did not obtain appropriate approvals from the Institutional Review Board and/or the Medical

---

106 TTS further explained: “Our standard practice is to keep close communication with inventors concerning their inventions, including letting them know if we have determined whether or not we will file a patent application. Because of the seriousness of the ongoing investigation and since we had determined that we were not going to file a patent application… we determined that our communication with the inventors should be stopped so as to not inadvertently cause any confusion to the investigators.” Exhibit 175.
CONFIDENTIAL

Staff for the second and third cases, we also believe that all of these surgical cases were physician-driven efforts to prolong the patients’ lives. These surgical cases involved the use of an unmarketed biologic and did not constitute ‘research,’ and therefore this did not fit squarely within then-existing policies and procedures governing human subject research and did not involve the delivery of investigational drugs or devices into the surgical setting…Most importantly, the surgeons did ensure that the patients and their families understood from the outset that the circumstances were extremely dire, that the procedure involved deliberately infecting the patient’s brain with the hope of triggering a localized and potentially beneficial immune response to attack the deadly form of brain cancer and was essentially untested, and thus that the potential outcomes were quite uncertain. Regrettably the patient’s succumbed to their disease.107

In another portion of the CMS Report, Dr. Siefkin noted as a clarification to that “[t]he innovative care provided to Patient 1 was approved by UCDMC leadership. It was recognized that the care was non-standard. The care was not experimental.”108

P. Patient Consent Forms

Below is a summary of the patient consent forms signed by Patients 1, 2 and 3. The IRB was not asked to review or approve these consent forms before they were provided to the patients.

1. Patient 1’s Consent Form, Exhibit 120

The consent form for Patient 1 was signed by Patient 1 and , as well as Dr. Schrot and Dr. Muizelaar at 2:30 PM on , 2010. The consent describes the procedure as implanting of “live gram negative bacteria into the tumor bed and around the bone flap.” The form further acknowledges all prior treatment of Patient 1 and projected life expectancy.

The form further notes the surgeons’ lack of experience with the treatment, stating that it may be “totally ineffective,” and that the procedure has not been tested or certified by the FDA or any other Federal or State agency. The form also states that the resulting infection may cause side effects such as “paralysis, inability to speak or understand speech, inability to swallow, vegetative state, coma or death.” The form does not state that Dr. Muizelaar and Dr. Schrot have

107 See CMS Report at 1A-1B, Exhibit 169.
108 Id. at 4S.
any financial or research interest in conducting the procedure. Patient 1’s surgery occurred on 

2. Patient 2’s Consent Form, Exhibit 128

The consent form for Patient 2 was signed by Patient 2, and Dr. Schrot at 2:40 PM on , 2010. The form echoes the language of the consent form for Patient 1 in describing the procedure and stating that there is no proof the treatment will be beneficial. The form also states that Patient 2 has undergone the standard treatment for glioblastoma.

The form repeats the language regarding lack of effectiveness and approval by the FDA or any other agency, and potential side effects. The form does not state that Dr. Muizelaar or Dr. Schrot have any financial or research interest in conducting the procedure. Patient 2’s surgery occurred on , 2010.

3. Patient 3’s Consent Form, Exhibit 132

The consent form for Patient 3 was signed by Patient 3, and Dr. Schrot without date or time. As with the consent forms for Patients 1 and 2, it describes the surgery and the lack of support or animal data showing any beneficial effect. The form further states that the patient is aware of the standard therapy for glioblastoma, and that the proposed procedure would disqualify the patient from clinical trials for which he or she might otherwise be qualified. The form describes the treatment of Patients 1 and 2 with the intentional wound infection procedure, noting the death of Patient 1, and “tumor regression” in Patient 2. The form provides the same potential side effects as the prior consent forms, as well as lack of FDA or other agency approval for the procedure.

Unlike the prior two consent forms, this form does explicitly grant Dr. Muizelaar and Dr. Schrot permission to publish any information learned in the course of treatment. The form does not, however, disclose any financial interest. Patient 3’s surgery occurred on 2011, Exhibit 134.

IX. ANALYSIS

The procedure that was performed on the three patients at UCD Medical Center involved the use of bacteria to create an intentional surgical wound in the brain for terminally ill glioblastoma patients. It is undisputed that during and before the relevant time period, there were no studies to substantiate the underlying theory of the procedure; instead the concept for the procedure was based on anecdotal evidence and the belief by some/many in the neurosurgery field that brain tumor patients with postoperative wound infections have prolonged survival
It is also undisputed that the procedure was a significant departure from the standard treatment provided to glioblastoma patients, which included surgery to reduce or remove the tumor, chemotherapy, radiation, and/or medication. Dr. Muizelaar and Dr. Schrot have maintained at all times that the procedure in question was not research; rather, it was used as innovative treatment to try to prolong the lives of the patients.

As discussed in greater detail below, I find that Dr. Muizelaar violated the Faculty Code of Conduct, APM 015, by engaging in conduct that constitutes a serious violation of University research policies. Specifically, Dr. Muizelaar violated APM 015 by failing to obtain the appropriate review and approval as required by UCD PPM 240-50 and FDA regulations. I further find that Dr. Muizelaar failed to adhere to the University of California’s Standards of Ethical Conduct.

A. History Regarding 2008 Patient

This history of what occurred in 2008, when Dr. Schrot and Dr. Muizelaar sought approvals for the use of the intentional wound infection procedure on the patient is critical because through those efforts, Dr. Muizelaar was made aware of the regulatory requirements, as well as the requirements of the UCDMC Bioethics Consultation Committee and IRB, related to the use of that procedure. Although most of the communications in that time frame were written by or to Dr. Schrot, Dr. Muizelaar had proposed use of the intentional wound infection procedure and prompted Dr. Schrot to initiate the approval process. Dr. Muizelaar was copied on several key communications, and the evidence suggests that he was made aware of the IRB’s and FDA’s recommendations thereafter by Dr. Schrot. Indeed, as Dr. Muizelaar knew, when Dr. Schrot first contacted Eric Mah to discuss the procedure for Patient 1 in 2010, the animal (rat) studies had already been in progress for more than a year. Dr. Schrot started developing the rat studies shortly after he and Dr. Muizelaar were unable to obtain IRB approval for the patient in 2008.

In 2008, the Bioethics Consultation Committee had concluded and informed Dr. Schrot that the IRB needed to review and approve the procedure. Shortly thereafter, Dr. Muizelaar and Dr. Schrot to Prof. Ikemoto and Melissa Jones that: “A specific ethics consult was not obtained for [Patient 1] since a full ethics committee review had already been convened previously in 2008 to discuss the proposed treatment of [the patient]. The [Bioethics] Committee had voted at that time to approve the treatment.” Letter at 8, Exhibit 168.

109 A survey that was published in 2009 by Bonham et al., regarding non-intentional infections in brain tumor patients concluded that “postoperative infection did not confer any survival advantage in patients with glioblastoma multiforme.” Exhibit 115.

110 According to Dr. Kon, the Bioethics Consultation Committee was uncomfortable with the proposed procedure and determined that there needed to be more oversight than the Bioethics Committee could provide. The Bioethics Consultation Committee specifically recommended that IRB approval would be required. This is contrary to the claim made in the letter from Dr. Muizelaar and Dr. Schrot to Prof. Ikemoto and Melissa Jones that: “A specific ethics consult was not obtained for [Patient 1] since a full ethics committee review had already been convened previously in 2008 to discuss the proposed treatment of [the patient]. The [Bioethics] Committee had voted at that time to approve the treatment.” Letter at 8, Exhibit 168.
CONFIDENTIAL

Asmuth, Co-Chair of the IRB, told Dr. Schrot that he needed to fill out “a full committee application,” (referring to the IRB) for approval regarding the procedure.¹¹¹ Dr. Muizelaar was not copied on Dr. Asmuth’s email but he was copied on the prior emails that informed him that Dr. Schrot was consulting the FDA and IRB on the proposed procedure. Although the procedure in 2008 was proposed for a [redacted] patient, after receiving guidance from the Bioethics Consultation Committee, Dr. Asmuth, Dr. Anderson and FDA, Dr. Schrot concluded that “the FDA cannot approve this trial in a human.”¹¹² Dr. Schrot and Dr. Muizelaar ceased efforts to proceed with the procedure for the patient on [redacted], 2008, and Dr. Schrot wrote in an email to the IRB Co-Chairs, Dr. Muizelaar, and others that the IRB application was “[suspended since the FDA, and hence the IRB, cannot currently approve the protocol without further preclinical studies to support the use of an IND.”¹¹³

Shortly thereafter, Dr. Schrot took steps to develop a rat study, including securing the use of a laboratory and hiring a graduate student to assist with the study. The evidence reflects that Dr. Muizelaar was aware of this proposal. He likewise stated in his interview that he knew at the time that the bacteria used in the study was procured from ATCC, located in Manassas, VA.¹¹⁴

¹¹¹ Email from Dr. Asmuth to Dr. Schrot copying others, dated [redacted] 2008, Exhibit 106. Dr. Muizelaar was copied on a portion of this email chain, but not the email from Dr. Asmuth to Dr. Schrot.

¹¹² Email from Dr. Schrot to Dr. Anderson and others, dated [redacted] 2008, Exhibit 109.

¹¹³ Email from Dr. Schrot to Dr. Anderson, Dr. Asmuth, Dr. Muizelaar and others dated [redacted] 2008, Exhibit 112 (emphasis added).

¹¹⁴ Dr. Lorena Navarro sent several emails to Dr. Schrot in [redacted] 2009, noting that the order for the bacteria had been placed and that she was waiting for it to arrive so she could culture it, Exhibit 114. Dr. Muizelaar stated in his interview for this investigation that he knew that the bacteria used in the study was ordered from the ATCC.

¹¹⁵ NIH Summary Statement at 2-4, Exhibit 117.

¹¹⁶ Id. at 3-4.
Dr. Schrot used a departmental grant to conduct the rat studies. It is, however, unclear whether Dr. Schrot shared the NIH’s comments with Dr. Muizelaar.

B. Patient 1

Dr. Muizelaar had discussed the idea of intentional wound infection with Patio 1, while Patient 1 received standard treatment at [REDACTED]. Dr. Muizelaar revisited the idea with Patient 1 in Fall 2012, and then asked Dr. Schrot to investigate the possibility of using the procedure on Patient 1 at UCD. Thus, in [REDACTED] 2010, Dr. Schrot approached Eric Mah, the then Director of the IRB, about the use of the procedure for Patient 1. He told Mr. Mah that the bacteria that would be used in the procedure was locally available and that the procedure would be offered as innovative treatment in the best interest of the patient. Mr. Mah said Dr. Schrot told him the patient represented a rare case and gave him the impression that it was a one-time request for this specific patient. Based on that information, Mr. Mah informed Dr. Schrot that the procedure did not require IRB review because it did not constitute human subjects research and because the bacteria was not from an outside source.\(^{118}\) Mr. Mah told him, “if your intentions to conduct human subjects research, IRB review and an IND application to the FDA may be required.”\(^{119}\) The evidence establishes that Dr. Schrot communicated this information to Dr. Muizelaar at the time.

On [REDACTED] 2010, Dr. Muizelaar forwarded the draft consent form for Patient 1 to Dr. Siefkin.\(^{120}\) Dr. Siefkin reviewed the consent form and sent a lengthy response on [REDACTED], 2010. Among other topics, Dr. Siefkin advised Dr. Muizelaar to obtain an Ethics consultation, consider potential complications from the treatment and related costs.\(^{121}\) In the email, Dr. Siefkin references the earlier conversation that he had with Dr. Muizelaar, in which Dr. Muizelaar referred to explained he was “planning this very rare (unproven) trial of one as a compassionate attempt to prolong

---

\(^{117}\) *Id.* at 6.

\(^{118}\) Email from E. Mah to Dr. Schrot, dated [REDACTED], 2010, Exhibit 119.

\(^{119}\) *Id.*

\(^{120}\) Email from Dr. Muizelaar to Dr. Siefkin, dated [REDACTED], 2010, Exhibit 121.

\(^{121}\) Email from Dr. Siefkin to Dr. Muizelaar and Dr. Schrot, dated [REDACTED], 2010 (9:26 AM), Exhibit 121.
CONFIDENTIAL

life..."

He also asked Dr. Muizelaar to “document in writing your conversation with the Human Subjects Chair who said ‘you can proceed as long as to talk with the CMO.’”

As discussed below, with regard to Patient 1, the advice provided to Dr. Schrot and Dr. Muizelaar was based on incomplete and inaccurate information provided by Dr. Schrot to Mr. Mah regarding the source of the bacteria and the intent to conduct the procedure on a single patient. This issue was exacerbated by Dr. Muizelaar’s representation to Dr. Siefkin that this procedure was proposed as a “trial of one.”

First, Dr. Schrot’s representation that the bacteria was available from a local source was not accurate. Dr. Schrot knew that the bacteria used in the procedure was ordered and received from ATCC in 2009, and that it had been grown in a UCD laboratory without modification. It is undisputed that the bacteria constituted an “unmodified descendent from the ATCC Materials,” and thus, was progeny of the material from ATCC. These facts demonstrate that the “source” for the bacteria was ATCC, not the local UCD laboratory. The expert consulted for this investigation, Dr. Robert Levine, agreed that under these circumstances, it was not reasonable for Dr. Schrot to consider the bacteria as locally available.

When responding to the IRB’s investigation in the fall of 2011, Dr. Schrot and Dr. Muizelaar acknowledged that their original interpretation was incorrect. They stated: “We no longer believe that application of bacteria to create an intentional wound infection falls outside the purview of the IRB and FDA, nor that the bacteria cultured for over a year in a UC Davis laboratory, but originally obtained from Manassas, VA, are considered ‘locally obtained.’” More recently, they have retracted that statement and Dr. Schrot and Dr.

122 Id.

123 Id.

124 Id.

125 The MTA defines “Progeny” as “an unmodified descendant from the ATCC Materials, such as virus from virus, cell from cell, or organism from organism.” Accordingly, even after the bacteria from the ATCC was grown in the laboratory at UCD, it remained the “progeny” of the biologic product from ATCC.

126 Confidential Response to IRB Findings from Dr. Muizelaar and Dr. Schrot, Exhibit 156. (Emphasis added.) Similarly, Dr. Schrot stated in a letter to Dr. Asmuth and Dr. Anderson, dated [redacted], 2011, that he did not intend to supply inaccurate information to the IRB regarding the source of the biologic and that he “did not explore the importance of the ultimate source of the seed cultures with the [IRB] Director at the time” and he had an “incomplete understanding of the definition of a locally obtained drug or biologic.” See Letter from Dr. Schrot to Dr. Asmuth and Dr. Anderson, dated [redacted], 2011, page 170 to FDA Report, Exhibit 155. (Emphasis added.)
Muizelaar have now asserted that: “[t]he determination that bacteria from a local laboratory are not in fact local if the seed cultures are from the ATCC is unprecedented, and flies against the advice previously given by Drs. Skip Nelson and David Asmuth in 2008.” However, nothing in the 2008 advice from Dr. Nelson or Dr. Asmuth addresses this issue directly or supports their interpretation. Dr. Schrot and Dr. Muizelaar also have not identified any policy, document, or guideline that supports their claim that it is “unprecedented” to conclude that the bacteria was not local. Moreover, their interpretation is discredited by their own admissions in the fall of 2011.

Even though Dr. Muizelaar was aware that the bacteria had been obtained from ATCC, there is no evidence that he directed Dr. Schrot to provide this information to Mr. Mah or that he made any effort to do so himself. Dr. Muizelaar may have had a good faith belief that the bacteria was from a local source in 2010. Nonetheless, given the importance of compliance with FDA regulations for the University, what he had learned in 2008 regarding FDA requirements, and his knowledge that the bacteria had been obtained from ATCC just one year prior, he should have considered and discussed this issue with Dr. Schrot and/or Mr. Mah. There is no evidence that he did so.

Second, the use of the bacteria from ATCC did not comply with the terms of the Material Transfer Agreement from ATCC, which stated that it was not intended for use in humans. Dr. Muizelaar likely did not see or read the MTA. Given that this procedure had never been conducted before, as the lead surgeon Dr. Muizelaar shared responsibility with Dr. Schrot for knowing whether the MTA placed any restrictions on its use. Such caution was particularly appropriate because Dr. Muizelaar knew that no product (including this strain of bacteria) had ever been used or approved for the purpose of creating an infection in the brain of a glioblastoma patient.

Third, the evidence suggests that by 2010, Dr. Schrot and Dr. Muizelaar were interested in developing the procedure as an innovative treatment for multiple glioblastoma patients, not simply as a treatment for Patient 1. For instance, the grant application that Dr. Schrot submitted for the rat studies stated in part: “This research tests the proof of concept that intracranial bacterial infection provides a therapeutic benefit in glioblastoma, providing a preclinical framework for human trials.” Similarly, the Protocol for Animal Care and Use that

127 Letter at 17, Exhibit 168.

128 The conclusion that bacteria used in Patient 1 was not local is consistent with the conclusion of the medical staff peer review and the IRB review.

129 He also knew from communications in 2008 with FDA that “[t]here are very stringent criteria for any biologic to be tested in a human, which include a list of about 9 criteria which need to be satisfied in an animal model.” See Email from Dr. Schrot to Dr. Anderson, dated, 2008, Exhibit 109.

130 Grant Application at Section 6, Project Summary/Abstract, Exhibit 113.
Dr. Schrot submitted for the rat studies noted: “Promising results in our pre-clinical investigations could open the door to FDA approved phase I clinical trials in humans, offering new hope to patients whose lives are otherwise cut short by this deadly tumor.” This evidence does not negate Dr. Muizelaar’s claim that he and Dr. Schrot believed that the procedure was the best treatment option for Patient 1. However, that they contemplated conducting the procedure on more than one patient is significant because Mr. Mah’s analysis and recommendation was based on his understanding that the procedure was intended for a single patient only. Mr. Mah’s belief is documented in his contemporaneous communication to Dr. Schrot on 2010. Similarly, Dr. Siefkin noted at the time that it was his understanding based on his conversation with Dr. Muizelaar that the procedure was planned as a “trial of one as a compassionate attempt to prolong life….” Dr. Muizelaar should have informed Dr. Siefkin that he and Dr. Schrot had larger goals for the procedure.

Finally, Dr. Schrot had been advised by the FDA in 2008 that “animal studies must show not only safety, but also establish a reasonable proof of concept in order for this investigational therapy to be introduced into patients.” Dr. Muizelaar was copied on an email in 2008 from Dr. Schrot in which he suspended the proposal, noting that the procedure “has been suspended since the FDA, and hence the IRB, cannot currently approve the protocol without further pre-clinical studies to support the use of an IND.” Dr. Muizelaar was thus well aware of the FDA’s requirement for pre-clinical studies regarding the proposed procedure. The animal studies that were in place in 2010 were not completed, and had not shown safety of the procedure or reasonable proof of concept. Indeed, it is questionable whether the studies ever would have been able to meet the FDA’s requirement to show “proof of concept” given that the NIH review had concluded that the study had “seriously flawed methodology and statistical analysis.” Dr. Muizelaar also did not have any reason to believe that the requirement for use of the procedure, which had never been conducted in a human previously, could be done on adults without

131 IACUC Protocol [Ex. 5 to FDA letter], Exhibit 159.

132 His communication in 2010, when Dr. Schrot approached him about Patient 2, also establishes that Mr. Mah understood the procedure for Patient 1 “was an extremely rare event with a terminally ill patient who was rapidly declining.” 2010 Email from Mr. Mah to Dr. Schrot, copying Dr. Muizelaar, Exhibit 124.

133 Email from Dr. Siefkin to Dr. Muizelaar and Dr. Schrot, dated 2010 (9:26 AM), Exhibit 121.

134 Ex. 111.

135 Email from Dr. Schrot to Dr. Anderson, Dr. Asmuth, Dr. Muizelaar and others dated 2008, Exhibit 112.

136 NIH Summary Statement at 2, Exhibit 117.
sufficient animal data, particularly where the UCD PPM provides that “whenever possible and relevant, animal research will precede research on human subjects.”

C. Patient 2

In 2010, Dr. Schrot contacted Mr. Mah regarding the procedure for Patient 2. Mr. Mah responded in an email, copying Dr. Muizelaar, noting that he was surprised by the request because he believed the procedure for Patient 1 was an “extremely rare event.” Mr. Mah again noted his understanding that the proposed procedure would entail use of “locally-grown bacteria.” He expressed concern that “[a]s you increase the number of patients, [] your activity could appear to be human research.” He referred Dr. Schrot (copying Dr. Muizelaar) to new FDA draft guidance, which he noted indicated that “the use of the bacteria would (in FDA’s eyes) be subject to their regulation, purview and authority.” Mr. Mah recommended that Dr. Schrot obtain consent from the patient and family regarding the “unconventional/innovative methods” and that he consult with the CMO, Dr. Siefkin, before performing the procedure. He concluded by noting in bold print: “if you anticipate another future patient will need this unconventional/innovative treatment, I recommend a treatment IND application be submitted to FDA and the protocol undergo IRB review, as appropriate, prior to the next procedure.”

The draft guidance that Mr. Mah provided to Dr. Schrot and Dr. Muizelaar contained information that should have alerted them that an IND would be required before proceeding with the procedure on Patient 2. Although the draft guidance had not been finalized, it described the FDA’s thinking on various topics and, in many instances, cited specific regulatory and statutory requirements that were already in place as of 2010. Among other points, the draft guidance confirmed that bacteria meets the FDA’s definition of a “drug” and that a clinical investigation could include as few as one subject. Having been provided with this draft guidance by Mr. Mah, Dr. Muizelaar was on notice of the FDA’s and the IRB’s interpretation of these issues and had ready access to summaries and citations to the relevant regulations.

After communicating with Mr. Mah, Dr. Schrot then emailed the graduate student to assist with preparation of the bacteria, noting that he “discussed the case with the director of the

137 UCD PPM 240, Section 50 at I.D.
138 Exhibit 124.
139 Id.
140 Id.
141 Id. (Emphasis in original).
142 FDA 2010 Draft Guidance at 9, 13, Exhibit 118.
UC Davis IRB and he has given us cautious clearance to do this."\(^{143}\) He then replied to Mr. Mah, copying Dr. Muizelaar, stating: “We completely agree that continued treatment should involve IRB approval in the context of a clinical trial, and we would absolutely like to move forward with conducting a pilot study.”\(^{144}\) He then quoted a portion of the FDA draft guidance and explained that unlike the procedure in the guidance, the procedure in question has a “therapeutic” purpose. However, Dr. Schrot then conceded that “it could be that, by extension, our proposed study would be considered to be a challenge study by virtue of ‘altering the structure or function of the body,’ and as such, would be regulated.” Mr. Mah replied, copying Dr. Muizelaar, noting that FDA has become more aggressive with IND and investigational devices and that he thought an “IND is sensible or at a very minimum” documentation from FDA that an IND is not required, and stating that he would put Dr. Schrot in touch with someone to assist with the IND application.

The 2010 emails regarding Patient 2 indicate that there may have been a misunderstanding between Dr. Schrot and Mr. Mah as to whether the procedure for Patient 2 would proceed. As the IRB investigation concluded, Mr. Mah believed at that time that no further patients would receive the procedure without IRB or FDA approval (including Patient 2), but Dr. Schrot believed at that time that he had “cautious clearance” to proceed with Patient 2.\(^{145}\) Taken in context, it was not unreasonable for Dr. Schrot and Dr. Muizelaar to believe that Mr. Mah had agreed that they could conduct the procedure on Patient 2, as long as the CMO approved and the appropriate consent was obtained.

It was made clear to both surgeons, however, that Mr. Mah had serious concerns with the proposal to conduct the procedure on Patient 2 and that Dr. Schrot and Dr. Muizelaar should consult with the CMO, Dr. Siefkin, before conducting the procedure.\(^{146}\) Dr. Schrot and Dr. Muizelaar did not do so. Dr. Schrot and Dr. Muizelaar admit that they failed to consult with Dr. Siefkin, but claim that they did not do so because “it was, after all not required, only recommended.”\(^{147}\) The decision not to consult Dr. Siefkin was not reasonable, especially given that Dr. Siefkin had himself expressed a long list of issues at the time Dr. Muizelaar had discussed Patient 1 with him.\(^{148}\) It also problematic because when he gave the tacit approval for

\(^{143}\) Email from Dr. Schrot to [redacted], dated [redacted], 2010, Exhibit 126.

\(^{144}\) Email from Dr. Schrot to Mr. Mah, copying Dr. Muizelaar, dated [redacted], 2010, Exhibit 125.

\(^{145}\) IRB Investigational Findings, Aug. 31, 2011, at 3, Exhibit 151.

\(^{146}\) Email from Mr. Mah to Dr. Schrot, copying Dr. Muizelaar, dated [redacted], 2010, Exhibit 119.

\(^{147}\) Dr. Muizelaar and Dr. Schrot Letter at 11, exhibit 168.
the procedure on Patient 1, Dr. Siefkin noted in his email that it was a “single trial,” a “trial of one,” for a “single case”—strongly suggesting that had he been consulted about the procedure for a second patient, he would have instructed Dr. Schrot and Dr. Muizelaar not to proceed.\textsuperscript{149}

Accordingly, in addition to the issues regarding Patient 1 that continued for Patient 2 (including the failure to provide Mr. Mah accurate information regarding the source of the bacteria, the failure to comply with the MTA from ATCC for use of the bacteria, and the failure to have animal data demonstrating the safety of the procedure and proof of concept), the decision to proceed with the procedure on Patient 2 without obtaining approval from Dr. Siefkin was contrary to the instructions from Mr. Mah, the IRB Director. This failure constituted a violation of UCD PPM Chapter 240 and the University of California Ethical Code of Conduct in Research, both of which require IRB review and approval. To the extent that Dr. Muizelaar seeks to rely on Mr. Mah’s emails from \textsuperscript{149}2010 to demonstrate that he had IRB approval, those same emails strongly communicated the need to consult with Dr. Siefkin before proceeding. It was not reasonable or appropriate for Dr. Muizelaar to consider Mr. Mah’s statement regarding consulting with Dr. Siefkin to be a mere “recommendation” that he could disregard. Therefore, Dr. Muizelaar did not seek or obtain the necessary approvals before conducting the procedure on Patient 2.

D. Patient 3

The evidence overwhelmingly establishes that Dr. Muizelaar knew that he did not have the necessary approvals from the IRB or the CMO to proceed with the procedure on Patient 3, but that he nonetheless did so. The evidence also establishes that he knew that he needed to obtain an IND before any procedures were conducted on any patients after Patient 2.

Mr. Mah’s \textsuperscript{150}2010 email stated: “I recommend a treatment IND application be submitted to FDA and the protocol undergo IRB review, as appropriate, prior to the next procedure.” Dr. Schrot responded, copying Dr. Muizelaar and noting that he and Dr. Muizelaar “completely agree that continued treatment should involve IRB approval in

\textsuperscript{148}Email from Dr. Siefkin to Dr. Muizelaar, copying Dr. Schrot and Anna Orlowski, dated \underline{2010}, Exhibit 121.

\textsuperscript{149}The evidence is not clear whether Dr. Muizelaar deliberately disregarded the statement by Mr. Mah that they should consult with Dr. Siefkin before conducting the procedure on Patient 2.

\textsuperscript{150}Email from Mr. Mah to Dr. Schrot, copying Dr. Muizelaar, dated \underline{2010}, Exhibit 124. (Emphasis added.)
the context of a clinical trial,” indicating his understanding of the IRB Director’s instruction.\(^{151}\) Even though Dr. Muizelaar now seeks to interpret Mr. Mah’s instruction for an IND application and IRB approval as mere suggestions, because he was copied on the communication to Mr. Mah his agreement that continued treatment should involve IRB approval in a clinical trial, Mr. Mah had no reason to clarify his response or take further action to stop Dr. Schrot and Dr. Muizelaar’s efforts to continue providing the procedure.

The contemporaneous communications establish that Dr. Muizelaar knew that he and Dr. Schrot needed to obtain an IND under FDA regulations before proceeding further, and that he knew the IRB likewise required that he obtain an IND. His failure to seek an IND before Patient 3 or otherwise discuss Patient 3 with the IRB and CMO was a serious violation of UCD policies and FDA regulations, including PPM 240-50, 21 CFR 312, and the University of California Ethical Code of Conduct in Research.

In addition, Dr. Siefkin directly instructed Dr. Muizelaar to obtain IRB approval after Patient 2 and before the procedure was conducted on Patient 3. Notably, as the Medical Staff Peer Review memorandum from Dr. Siefkin noted:

This Medical Staff Peer Review memorandum was issued to both Dr. Muizelaar and Dr. Schrot, and neither objected to this statement as inaccurate at that time.\(^{153}\)

Had Dr. Schrot and Dr. Muizelaar submitted an IRB application before proceeding with the procedure for Patient 3, the evidence is clear that the IRB would not have allowed the procedure to be conducted on Patient 3 without further involvement/approval from the FDA. Mr. Mah had communicated as much to Dr. Schrot and Dr. Muizelaar in [REDACTED] 2010, noting

\[^{151}\text{Email from Dr. Schrot to Mr. Mah, copying Dr. Muizelaar, dated [REDACTED], 2010, Exhibit 125.}\]

\[^{152}\text{[REDACTED], 2011, Peer Review Memorandum from Dr. Allan D. Siefkin, CMO, Exhibit 147.}\]

\[^{153}\text{Dr. Muizelaar has informed us during this investigation that Dr. Siefkin never told him not to proceed with a third patient. But, as noted above, this fact was included in the peer review memorandum and the IRB Investigation Findings. Indeed, the IRB’s Investigation Findings, dated August 31, 2011, stated that after patient 2, “Subsequent discussions result in an explicit directive from the CMO not to proceed with any additional cases absent IRB approval.” Id. at 3 (emphasis added). Dr. Schrot and Dr. Muizelaar wrote a three page memorandum responding to the IRB’s findings and never disputed the statement that the CMO had issued an explicit directive not to proceed with any additional cases after Patient 2. Accordingly, I conclude that their claim that Dr. Siefkin never made this statement is not credible.}\]
his concern that the decision to conduct the procedure on multiple patients made the activity “appear to be human research” and that the new FDA draft guidance suggested that it would view the bacteria as subject to FDA “regulation, purview and authority.”

During his interview for this investigation, Dr. Anderson also noted that he referred Dr. Schrot to the FDA in 2008 because he saw “red flags” with regard to the proposed procedure. Dr. Anderson also noted that the FDA’s definition of research has gray areas and even if it may not be human subjects research, it was the type of procedure that should still be reviewed by the IRB. Dr. Anderson also stated that he did not see what would be different in 2010 than in 2008, when the IRB had sent Dr. Schrot to the FDA. Similarly, Dr. Asmuth said he made it clear in 2008 that the procedure would require an IND. During this investigation, he called the use of the procedure by Dr. Muizelaar and Dr. Schrot the worst case of human subjects research he had ever seen.

Further, Dr. Schrot and Dr. Muizelaar were unable to offer any reasonable explanation for their attempt to convene the Ad Hoc Ethics Committee given the existence of the IRB and Bioethics Committee at UCD, which also suggests that they were seeking a way to circumvent the IRB process. Dr. Schrot noted in the email sending the Prospectus that the committee had been established at the “behest of Fred Meyers, MD, MACP, Executive Associate Dean of the UC Davis School of Medicine,” which Dr. Meyers adamantly denied. Also problematic is that the Prospectus contained misleading statements that “additional discussion” had occurred with the hospital staff before the procedure was conducted on Patient 2 and 3, implying that hospital staff approved the procedures, which had not occurred. This additional conduct was improper and did not comply with the obligation in the Ethical Code of Conduct that all research be conducted “with integrity and intellectual honesty at all times.”

Finally, before the procedure was conducted on Patient 3, Dr. Muizelaar and Dr. Schrot submitted a Record of Invention regarding the procedure to the Technology Transfer Services, the initial step to obtaining a patent. It does not appear likely that a patent would be available for the procedure, and it likewise does not appear that either doctor anticipated any financial benefit related to their “invention” of the procedure. Nonetheless, the consent form for Patient 3 should have disclosed the potential financial interest of Dr. Schrot and Dr. Muizelaar in light of their then-pending ROI application. The failure to disclose this potential conflict did not adhere to the University of California’s policy that “community members are expected to take appropriate steps, including consultation if issues are unclear, to avoid both conflicts of interest and the appearance of such conflicts.”

154 Email from Mr. Mah to Dr. Schrot, copying Dr. Muizelaar, dated [redacted], 2010, Exhibit 124.

155 Prospectus at 4, 5, Exhibit 136.
E. Response to Issues Raised by Dr. Muizelaar

Dr. Muizelaar, through his counsel and Dr. Schrot’s counsel, has raised several issues that I address here.

1. Research vs. Innovative Care

Dr. Muizelaar contends that no violation of the Code of Conduct occurred because the procedure was not “human subjects research” and thus, IRB approval was not required. To support this assertion, he referenced a scholarly article by John Lantos, which noted in the article summary that the difference between research and innovative therapy is based on the goals rather than the risks or newness of the therapy.\footnote{The 1994 article by Dr. Lantos simply explored the potential need to redefine research and treatment; it did not provide an analysis of existing regulations or legal authority and thus, is of limited value, Exhibit 100.} Dr. Muizelaar notes that the conduct in question should not be considered research because they did not intend to conduct research on the patients, did not intend to publish the results of the treatment, and did not enroll the patients in any research protocol.\footnote{Exhibit 168.} He further argues, through his counsel, that UCD has taken the position in the CMS report that the treatment was “non-standard, innovative care” and that UCD cannot take an inconsistent position in this investigation.

I have reviewed all of the evidence, discussed the issue of the definition of “research” with the expert consultant, and reviewed the relevant UCD policies and FDA regulations and guidance. I note that in cases involving procedures that have not previously been validated, the Belmont Report assigns responsibility to the institution to determine under what circumstances, if any, the procedure can be used at the institution. Here, the conduct of Dr. Muizelaar regarding the use of the procedure in the three patients clearly met the University’s definition of “research.” Specifically, the UCD PPM, Chapter 240, contains a broad definition of research and provides several examples that are applicable here. It states that “[t]he use of an investigational drug or device automatically identifies an activity as research”—bacteria, which had never been approved for the intentional wound procedure—was an investigational drug\footnote{FDA 2010 Guidance, which was provided to Dr. Schrot, states at page 9 that bacteria and other live organisms is a “biological product (see 21 CFR 600.3(h)(1)) and a drug, and an IND is required for the clinical investigation.” Exhibit 118.} and thus its use was automatically deemed “research” under the PPM.\footnote{Id. at V.G.1 (emphasis added).} Chapter 240 also states that a “surgical procedure is considered to involve research” if the “investigator wishes to develop a procedure that has not previously been performed,” or if he “wishes to study a
procedure that is not accepted therapy or that might not be considered ‘best medical care.’”
Again, the surgical procedure fell within these definitions of research since the procedure had not been previously performed on patients, was not an accepted therapy for the treatment of glioblastoma, and might not be considered “best medical care.”

In addition, the FDA regulations regarding INDs explain that a clinical investigation is an “experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of [the IND regulations], an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.”

The bacteria met the FDA’s definition of a drug. Furthermore, the FDA had specifically advised Dr. Schrot that “proof of concept” was required before the procedure could be conducted in humans and he shared the requirement for pre-clinical studies with Dr. Muizelaar after so being advised.

Neither UCD’s policy, nor the FDA’s regulations, depend on the intent of the doctor providing the procedure. They likewise do not depend on whether the patient is receiving the procedure as a treatment. Thus, that Dr. Muizelaar may not have intended to conduct research on the three patients is not determinative. Moreover, the issue of intent is not clear from the evidence here, particularly in light of the rat studies, Dr. Schrot’s application for an NIH grant, the ROI submission, and the request to the Ad Hoc Ethics Committee for approval to conduct the procedure on up to five additional patients.

With regard to the CMS Report, the CMO’s response included the following statement:

While we agree that the surgeons did not obtain appropriate approvals from the Institutional Review Board and/or the Medical Staff for the second and third cases, we also believe that all of these surgical cases were physician-driven efforts to prolong the patients’ lives. These surgical cases involved the use of an unmarketed biologic and did not constitute ‘research,’ and therefore this did not fit squarely within then-existing policies and procedures governing human subject research and did not involve the delivery of investigational drugs or devices into the surgical setting….

---

160 Id. at V.H., V.H.2-4.

161 21 CFR 312.3(b).

162 See, e.g., FDA 2010 Guidance at 10, Exhibit 118, (“‘There seems to be a belief among some investigators and IRBs that the IND regulations do not apply to clinical investigations that are not intended to investigate a drug’s potential for commercial sale. This belief is not correct. Whether the IND regulations apply to a planned clinical investigation does not depend on whether the intent of the clinical investigation is commercial or noncommercial.’”)
This statement acknowledges that Dr. Muizelaar did not obtain the appropriate approvals from
the IRB and/or medical staff for Patients 2 and 3, which is consistent with the conclusions
reached in this report. I do not agree that CMO’s statement that the care was not “research”
compels a conclusion that no Code of Conduct violations occurred. The CMO’s discussion of
the term “research” appears to be based on the FDA’s definition of research: “a systematic
investigation, including research development, testing and evaluation, designed to develop or
contribute to generalizable knowledge.”163 The definition of the term “research” in UCD’s
Policy and Procedure Manual is broader and demonstrates that Dr. Muizelaar was required to
obtain IRB approval.

Our expert consultant noted that the federal regulations do not define any procedures as
research. Rather, they define circumstances in which research must be done to evaluate the
safety and efficacy of a drug. The FDA regulations specify this requirement when, as in this
case, the drug is, or ought to be, classified as an investigational new drug. Significantly,
however, even if one assumes Dr. Muizelaar’s conduct did not meet the definition of “research,”
it does not change the conclusion that the evidence established that he was required to obtain
IRB and CMO review and approval before the procedures could be used on Patients 2 and 3 and
that he knew of these requirements. Again, this is consistent with the CMO’s statement in the
CMS Report. The requirement for IRB and CMO approval for Patients 2 and 3 was consistent
with UCD’s policies and procedures regarding human subject research, the conclusion of the
Bioethics Consultation Committee, and the recommendation of the IRB Director. It was also
consistent with the FDA’s specific advice given to Dr. Schrot in 2008 and the FDA’s Draft
Guidance, which Mr. Mah sent to Dr. Muizelaar in 2010. Consequently, Dr. Muizelaar’s attempt to assert that he did not need IRB approval based on his interpretation of
“research,” does not modify my conclusion that he violated the Code of Conduct.

2. Statement of Dr. Skip Nelson in 2008

Throughout this investigation, Dr. Schrot and Dr. Muizelaar have cited the email of FDA
Pediatric Ethicist, Robert “Skip” Nelson, as a basis for their assertion that they did not need IRB
review or approval for the use of the procedure on the three patients. Having reviewed all of
the evidence, I conclude that their characterization of the email of Skip Nelson is misleading. Dr.
Nelson was contacted by Dr. Schrot on 2008, regarding the proposed use of the
procedure on the patient. The email from Dr. Schrot was two paragraphs and provided
a brief summary of the proposed procedure, also noting that the ethics committee had given a
“thumbs up, pending IRB approval.”

Dr. Nelson replied by email on the same day, writing a total of six sentences. He noted
that “If the product you plan to use is available to you, I would suggest you proceed under the

163 45 C.F.R. § 46.102(d) (2009).
strategy of innovative treatment rather than research.”  He noted that he was “not familiar with
the literature on which you propose” and stated that if it is “only available under an IND, you
would need to work through CBER.” He then noted that he was leaving “for vacation in the
morning” and that he was copying Sara Goldkind at FDA to “help you negotiate through the
FDA process.”

Dr. Schrot then had a series of follow-up communications with others at the FDA, which
ultimately led to his conclusion that there was “very stringent criteria for any biologic to be
tested in a human,” including an animal model, and thus, “the FDA cannot approve this trial in a
human.”

The suggestion that was made by Dr. Nelson in his brief email regarding “innovative
treatment” was made in quick response to Dr. Schrot’s email, as Dr. Nelson left for vacation. He
specifically referred Dr. Schrot to someone else at FDA to “negotiate through the FDA process,”
which resulted in Dr. Schrot concluding that the FDA would not allow him to conduct the
procedure in a human. Thus, it is not reasonable for Dr. Schrot or Dr. Muizelaar to claim that
they relied on the statement of Dr. Nelson, nor is there any evidence that they actually did so.
Consequently, Dr. Nelson’s statement does not change my analysis and I conclude that it does
not excuse Dr. Muizelaar’s failure to obtain the required approvals for the use of the procedure in
the patients.

X. CONCLUSION

In light of the foregoing issues and discussion, it is my conclusion that Dr. Jan Paul
Muizelaar violated the Faculty Code of Conduct.

164 The product was not locally available to Dr. Schrot at that time and was not even
available as a progeny of the ATCC product as of [redacted] 2008. It was thus only available under an
IND.

165 Exhibit 109.