Inquire Committee Report Regarding
Allegations of Research Misconduct Against Professor Thomas Sutula

Allegations and Institutional Charge:

Dr. Steven Kriegler alleges that Professor Thomas Sutula, Professor and Chair, Department of Neurology and Director of the Center for Neuroscience has engaged in research misconduct as follows:

1. Dr. Kriegler alleges that Professor Sutula has engaged in "plagiarism" in two separate instances by not including Kriegler as an author on:

    a. A published abstract entitled "Novel anitconvulsant, antiepileptic properties and favorable toxicology provile of 2-deoxy-D-glucose (2DG in experimental models of epilepsy", submitted to American Epilepsy Society, December 2006 by Thomas Sutula *et al.* (see email from Kriegler dated September 19, 2006).
    b. A second publication entitled "2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure", *Nature Neuroscience*, Vol. 9, number 11, pages 1382-1387, November 2006 by Garriga-Canut *et al.* The corresponding author on this publication is Avtar Roopra, Assistant Professor of Neurology (see email from Kriegler dated October 20, 2006).

2. Dr. Kriegler (see email dated November 21, 2006) has alleged that a figure in the *Nature Neuroscience* (2006) publication referred to above "is graphed using the wrong axis to make it appear that 2DG is much stronger at preventing the progression of epilepsy than it really is". The committee needs to determine whether "falsification" of research data has occurred in the presentation of this figure.

PHS Support:

Dr. Sutula is an author on the American Epilepsy Society abstract and the *Nature Neuroscience* publication cited above and his PHS research grant (NINDS RO1 25020) is referenced for both publications. The inquiry committee considered both UW's and PHS's current regulations defining "research misconduct".

Policies and Procedures Regarding Allegations of Research Misconduct:

To evaluate whether research misconduct was engaged in under PHS's regulation, the inquiry team must answer the following requirements for finding of misconduct (42 CFR 93.104):

a. There must be a significant departure from accepted practices of the relevant research community.
b. The misconduct must be committed intentionally, knowingly or recklessly; and
c. The allegation must be proven by a preponderance of the evidence.

PHS defines **Research Misconduct** as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results ... *Research misconduct does not include honest error or differences of opinion."*

UW-Madison's policy adds to the definition, "...other practices that seriously deviate from those that are commonly accepted within the scholarly community for proposing, conducting or reporting research .. *It does not include honest error or honest differences in interpretations or judgments of data.*"

Plagiarism *is the appropriation of another person's ideas, processes, results or words without giving appropriate credit.*

Falsification *is manipulating research materials, equipment or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.*

Research Records and Evidence:

- The committee interviewed and corresponded by email with Dr. Steven Kriegler, the complainant and former Assistant Scientist in Department of Neurology. Dr. Kriegler also provided an electronic copy of a spreadsheet, the data of which was used to generate **Fig. 2A** of published US patent #0287253A1 entitled "Compounds and methods for treating seizure disorders" with S. Kriegler, A. Roopra, T. Sutula and C Stafstrom listed as co-inventors.
- The committee interviewed the four co-authors on the 2006 American Epilepsy Society abstract, each of whom were also included as co-authors on the 2006 *Nature Neuroscience* publication. In the order listed, these authors include: Dr. Thomas Sutula, Professor and Chair of Neurology, Mr. Jeff Ockuly, Research Specialist in Neurology, Dr. Carl Stafstrom, Professor of Neurology, Dr. Avtar Roopra, Assistant Professor of Neurology.
- The committee reviewed an abstract submitted to the American Epilepsy Society (AES) in 2005 co-authored by C. Stafstrom (communicating author), S. Kriegler, M. Valley, J. Ockuly, A. Roopra and T. Sutula (in order listed) entitled: "2-Deoxyglucose exerts anitconvulsant and antiepileptic actions in experimental epilepsy models". Dr. Fillingame, inquiry committee chair, interviewed Matt Valley (one of the co-authors by phone) to confirm the periods of time that he worked as an undergraduate in the Neurology department and his role in the experiments described in the 2005 AES abstract. Mr. Valley is currently a graduate student at Penn. State University.
- Dr. Fillingame interviewed Ms. Simone Dustin who worked part time in the Neurology department as an undergraduate, or did undergraduate research there, over the period 2001-2004. Ms. Dustin is presently in her 3rd year of medical school at UW and is doing her clinical clerkships.
- The committee reviewed Patent #0287253A1 with Kriegler, Roopra, Sutula, and Stafstrom listed as co-inventors and published in 2006.
- The committee also reviewed a patent application provided by Dr. Kriegler entitled "Compounds and methods for treating seizure disorders" on which he is listed as a sole inventor.

- The committee examined Dr. Kriegler's lab books on electrophysiological studies with hippocampal brain slices, which were provided by Dr. Stafstrom.

Regarding the charge of plagiarism for non inclusion of Kriegler as a co-author on the 2006 AES abstract (Allegation 1.a): The inquiry committee independently asked the four co-authors of the abstract for reasons why S. Kriegler and M. Valley were included as co-authors on the 2005 AES abstract but not on the 2006 AES abstract. The consistent answer was that neither Kriegler nor Valley had contributed to any of the experiments described in the 2006 AES abstract, experiments which were on the poster that was presented at the 2006 AES meeting (Dr. Stafstrom provided a copy of the poster). Rather the abstract and poster contradicted conclusions given in the 2005 AES abstract regarding the anticonvulsive/antiepileptic effects of 2DG. The contradictory data was attributed to experiments that were done by Kriegler, or in which he was involved in the analysis, that proved to be erroneous (detail are discussed below). Matt Valley's undergraduate research, done with Kriegler and Stafstrom, on the effect of replacing glucose with lactate, pyruvate and β-hydroxybutyrate on the electrical "bursting" response of hippocampal brain slices was cited in the 2005 AES abstract. This work is also part of the content of a manuscript that is currently being written, which includes Kriegler and Valley as co-authors and Strafsrom as first author. A copy of this manuscript was provided by Dr. Stafstrom.

The experiments in the 2006 abstract and poster contradict/refute two claims made in the 2005 AES abstract. The first is that 10 mM rather than 1 mM 2DG is required for suppression of the hippocampal slice electrophysiological bursting response. On examining Dr. Kriegler's lab books, the first entry regarding use of 2-DG in brain slice experiments is in November 2003 where he has written "1 mM 2DG". However, there are no details of how the experiment was set up. For example, the concentration and volume of the 2-DG stock solution added to the brain slice medium, and the volume and composition of the brain slice medium were not described. All of the notebooks examined lack similar details and are inadequate as scientific records. In our interview with Jeff Ockuly he indicated that all of the brain slice experiments with 2DG had to be repeated because it was impossible to match the lab book entries with the files of electrophysiological recording that are on the lab computers. Ockuly was responsible for repeating these experiments for the forth coming manuscript that is in preparation. To repeat, Kriegler and Valley are included in this this forth coming manuscript as co-authors because they did contribute the data on alternate energy sources to glucose in the brain slice medium.

The second error in the 2005 AES abstract that was corrected in the 2006 AES abstract is the conclusion that 2-DG raises the olfactory bulb electrical stimulation threshold necessary to evoke after stimulation discharges (ADs) in kindling experiments with rats. It was asserted in the 2005 AES abstract that 2-DG treatment raised the olfactory stimulation threshold, and this claim was based upon the Fig. 2A in the published Patient #0287253A1, which was generated by Kriegler from his analysis of some of the initial kindling experiments. The data supporting this figure could not be found in the lab, but the figure was included in the final patent that was published in 2006 anyway. There are several details here that bear on the question of why Kriegler was not included as co-author in either the 2006 AES abstract or the 2006 *Nature Neuroscience* paper.

- The correspondence regarding the initial patient application indicates that Kriegler wrote that the first experiments suggesting that 2DG increased the AD threshold were done by olfactory bulb stimulation.

- Lab records supporting 2DG effects on olfactory stimulation and the effect on AD threshold that would have been done in 2003 cannot be found. Such records should be available if the experiments were done since the lab has routine sign-in procedures for the undergraduate students who perform the surgeries and do the daily kindling stimulation. Jeff Ockuly oversees/supervises the collection and recording of this data.
- Stimulation via the perforant pathway was not mentioned in the initial patent application to WARF. It was subsequently shown that perforant pathway stimulation did increase the AD threshold, and in the final Patent #0287253A1, this data is included in Fig. 2B. In our interview with Dr. Kriegler, he acknowledged that he had nothing to do with the generation of this figure. The equivalent of Fig. 2B in the final published patent is also published as Fig. 1A in the *Nature Neuroscience* paper.
- In 2006, the lab re-initiated experiments using olfactory bulb stimulation to evoke ADs in the kindling experiments and found that the AD threshold in 2DG treated animals decreases during repeated stimulation as it does in normal control animals. This is opposite to Kriegler's initial conclusion, and this data was included in the 2006 AES abstract.
- During our inquiry, Kriegler provided a spreadsheet with the data used to generate Fig. 2A of Patent #0287253A1. He brought a copy of the figure with him to the interview. During our interview Kriegler stated that this data was generated by perforant pathway stimulation. We then showed him the Fig. 2A from the patent and the legend indicating that the figure was generated from olfactory bulb stimulation. Later that day (February 27, 2007), Kriegler emailed Dr. Fillingame and agreed that the data in the spreadsheet was from olfactory bulb pathway stimulation.
- On doing a more detailed analysis of the spreadsheet, the inquiry committee identified the names of the animals used in the experiments. Four animals had been subjected to 2DG treatment and five animals used as controls. Jeff Ockuly's lab records indicated that three of the four 2DG treated animals had surgeries for perforant pathway stimulation. A record on the fourth 2DG treated animal cannot be found. On the other hand, the five control animals had surgeries for olfactory bulb pathway stimulation. The experimental comparison that is published the patient Fig. 2A. is totally invalid. The confusion or mixing of experimental animal types may explain why Kriegler believes he had a role in the initiation of kindling experiments for both the olfactory bulb stimulation and perforant pathway stimulation.
- Because records were not available, Drs. Stafstrom, Roopra, Sutula and Jeff Ockuly all thought that Kriegler's initial analysis of kindling data was only of olfactory bulb stimulated animals as represented by Fig. 2A in the patent. Based upon their 2006 follow-up experiments, they also thought that the initial data was wrong, but because the data was not available, had no way of ascertaining why.

Regarding the charge of plagiarism for non inclusion of Kriegler as a co-author on the 2006 *Nature Neuroscience* paper (Allegation 1.b): Dr. Roopra (the communicating author), Dr. Sutula (the co-senior author), and co-author Dr. Stafstrom were all asked why Dr. Kriegler was not included as a co-author since he claims to have played a role in the initiation of the kindling experiments. All three state that Kriegler was not included because he did not contribute any of the experimental data that was published in the paper. The inclusion or exclusion of co-authors was decided upon by Drs. Roopra and Sutula, who served as senior authors on the paper. In their judgment each co-author had to have made a significant experimental or conceptual contribution to the paper. In their judgment, Kriegler did not meet the significant contribution criteria,

although he was involved in some way in the initiation of the kindling experiments. We have concluded the following:

- There is a consensus agreement amongst those that we interviewed that Dr. Roopra made the initial suggestion to use 2DG to inhibit glycolysis. Drs. Stafstrom and Sutula believe that the lab meeting where this suggestion was made took place in late Spring or early Summer of 2003.
- The suggestion was a logical extension of the antiepileptic effects of the ketogenic/low glucose diet being studied by Stafstrom's group, and the anticonvusant effects of replacement of glucose by lactate and other energy substrates seen in the brain slice experiments reported upon by Matt Valley in a lab meeting at the likely date of August or September 2002.
- There is disagreement in the recollections of each party's contribution to the initiation of the kindling experiments.
- Sutula believes that the perforant stimulation kindling experiments, published in the *Nature Neuroscience* 2006 paper, were initiated primarily via meetings between Sutula, Ockuly and Roopra, shortly after the suggestion to use 2DG was made by Roopra. He does not believe that Kriegler played a significant role in the design of these experiments. Further Kriegler's initial graph on the putative olfactory bulb stimulation experiments (Fig. 2A of the patent), which Dr. Sutula assumed had been done, had proven to be wrong.
- Kriegler believes that he played an important role in initiating the kindling experiments via an experiment where he directed an undergraduate student, Simone Dustin who was working under Dr. Stafstrom, to inject 2DG into a rat with the hope that the 2DG would make the rat ketotic. Dustin was instructed to go to the literature to find an appropriate dose; that dose and subsequent increases in the dose did not affect the rat's behavior, weight gain or make the rat ketotic. From this experiment with a single rat, Kriegler concluded that 2DG was not toxic and could be used in long term kindling experiments. He then requested that Jeff Ockuly initiate such experiments. Further, he recalls having Simone Dustin write a protocol for other undergraduate students to use in the 2 DG injections for the 2DG treated rats. Simone Dustin does not recall participation in the 2DG kindling experiments.
- Jeff Ockuly recalls that Kriegler may have suggested that they look at the effect of 2DG in the rat kindling model. This suggestion likely followed the Simone Dustin experiment on the effect of 2DG with the single rat.
- The importance of the single 2DG experiment done by Dustin and Kriegler is unclear and the notebook describing her observations cannot be found. The long term toxicity data on 2DG, generated by experiments on multiple rats and published in the 2006 *Nature Neuroscience* paper, was done by Jeff Ockuly without input from Kriegler.
- In our interview with Dr. Kriegler, the inquiry committee asked why he should be co-author on the 2006 *Nature Neuroscience* paper, particularly if it was true that he had not contributed to any of the experiments published in the paper. Dr. Kriegler stated that the initial experiment on 2DG injection with a single rat, which he had asked Simone Dustin to carry out, provided the incentive/impetus for the group to go forward with the kindling experiments. He had also instructed Simone Dustin to provide a protocol for 2DG injections in doing the experiments.
- Dr. Sutula claims to have overseen initiation the perforant stimulation pathway kindling experiments, having selected a dose of 2DG from the literature, without consultation with Kriegler about the Dustin single-rat experiment.

- In an email in the afternoon subsequent to our interview with Kriegler (on February 27, 2007) Kriegler claims to have played an instrumental role in development of the 2DG treatment protocol by changing the timing of the first 2DG injection to immediately after the rat's first AD, rather than after the 3rd AD. None of the experiments performed by the students supervised by Jeff Ockuly utilized such a protocol. Rather, each rat was subjected to stimulations evoking 3 ADs before the first injection of 2DG.

Concerning the allegation of *falsification* that a figure in the *Nature Neuroscience* (2006) publication is graphed using the wrong axis to make it appear that 2DG is much stronger at preventing the progression of epilepsy than it really is:

Dr. Kriegler was concerned that the data being plotted on the X-axis of Fig. 1A and on the Y-axis of Fig. 1B was "stimulation number" rather than "AD number". His reason for concern had to due with Fig. 2A of Patent #0287253A1. In the Fig. 2A that Dr. Kriegler had originally submitted with the initial patent application, he had plotted "relative AD threshold" (Y axis) versus "stimulation number" (X-axis). In the final version of the patent application, Dr. Sutula changed the labeling of the X-axis from "stimulation number" to "number of ADs" without correction of the data points in the figure, or the numerical scale on the X-axis. In Sutula's judgment, reporting number of ADs on the X-axis is the most appropriate way to report such data; Kriegler may have disagreed and may still disagree. Dr. Sutula regrets making the change in axis labeling since it introduced errors into the patent figure. [This may have been done because the primary data used to generate the figure was not available in the lab.] Currently Fig. 2A is being retracted from the patent, both because the axis is incorrectly labeled and the conclusion that the AD threshold increases in the 2DG treated, olfactory bulb stimulated rats is not correct.

In regard to Fig. 1A and 1B in the *Nature Neuroscience* 2006 paper, Dr. Sutula has confirmed that the numbers plotted are "AD numbers" and not "stimulation number". Further, at our request Jeff Ockuly has calculated the ratio of ADs/stimulation in 2DG treated rats and has shown that it decreases slightly over the average course of a kindling experiment relative to the controls. Hence, if stimulation number had been plotted on the Y-axis of Fig. 1 B, it would have over-emphasized rather than under-emphasized the anti-epileptic effects of prolonged 2-DG administration. This is opposite to the contention of Dr. Kriegler. At our interview with Dr. Kriegler, he agreed that if true AD numbers were plotted on the axes of Fig. 1A and AB, then the figures would not be misleading.

At the interview, Dr. Kriegler also expressed concern about what was being done with animals that initially had high AD thresholds, and if they were eliminated from the study that it would distort the results. We consulted Dr. Sutula and found that randomized data on all animals was retained in the study according to standard protocol, and all animals are reported in Fig. 1A and 2A of the *Nature Neuroscience* paper. Some of Dr. Kriegler's reservations about the experiments seem to involve reasonable scientific concerns about the design of the study and do not extend to the arena of scientific misconduct and falsification.

Statement of findings:

Allegation 1.a: *plagiarism* by non inclusion of Dr. Kriegler as co-author on 2006 AES abstract. Inquiry committee conclusion: **Allegation of scientific misconduct is clearly incorrect.** The abstract did not include any experiments that could be attributed to Kriegler. The abstract contradicted two conclusions that were attributed to Kriegler's experimental analysis in the 2005 AES abstract. The 2006 abstract is described as work to "further" characterize the anticonvulsant and antiepileptic properties of 2DG first reported in the 2005 AES abstract on which Dr. Kriegler was an author. The 2006 abstract reported on results that were from studies performed after Dr. Kriegler left the lab on September 30, 2004. It should be noted that abstracts submitted for presentation at meetings of scientific societies are, in general, reports on work in a particular inclusive period of time between meetings. Authors from previous abstracts need not be included in newer abstracts if no contribution can be attributed to those authors even though concepts and ideas for the work originated in the earlier abstract. This clearly is the relationship between the 2005 and 2006 AES abstracts.

Allegation 1.b: *plagiarism* by non inclusion of Dr. Kriegler as co-author on 2006 *Nature Neuroscience* paper. Inquiry committee conclusion: **Allegation of scientific misconduct is clearly incorrect.** The 2006 *Nature Neuroscience* paper did not include any experimental data that could be attributed to Kriegler. The senior authors, Roopra and Sutula, made a scientific judgment on the possible significance of any conceptual contributions made by Dr. Kriegler to the kindling experiments reported in the paper and concluded that his involvement did not warrant inclusion as a co-author. The decision to exclude Dr. Kriegler as a co-author does not represent a significant departure from accepted practices in the biological/medical research community at UW-Madison, or elsewhere. Disagreements regarding appropriate co-authors on scientific papers are a frequent source of debate in the scientific community[1]. Dr. Kriegler may have an honest difference of opinion on the value of his contributions and disagee with with the decision reached by the senior authors, Dr. Sutula (the PI of the PHS grant) and Dr. Roopra (the communicating author), who have the prerogative of assigning authorship.

In summary, Dr. Kriegler's charges of ***plagiarism*** based upon non-inclusion as an author are concluded to be incorrect in that procedures for assigning authorship to these publications did not deviate from commonly accepted practices for reporting research in the scholarly community.

Allegation 2: *falsification* in plotting appropriate data in Fig. 1A and/or Fig. 1.B of 2006 *Nature Neuroscience* paper. **Allegation of scientific misconduct is clearly incorrect.** The appropriate data were plotted as AD number on the axes of these figures and do not represent a misrepresentation of the data or of the prolonged antiepileptic effects of 2DG.

Final conclusion: We found no evidence that any of the co-authors of the 2006 AES abstract or 2006 Nature Neuroscience paper engaged in scientific misconduct related to the charges of plagiarism and falsification made in this complaint.

[1]*Guidelines published by the International Committee of Medical Journal Editors specify the following criteria for authorship: "Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual contents; and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3."*