Investigation into the research of Milena Penkowa

Final report by an international panel
23 July 2012

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Contents:

1. Introduction and summary

1.1 Introduction

This report presents an independent investigation into the research of Milena Penkowa. The investigation was initiated by University of Copenhagen in summer 2011 due to doubts about the honesty of the scientific production of Milena Penkowa. The aim of the investigation has been to clarify whether – and, if so, to what extent – questions about the scientific honesty of Milena Penkowa's research can be raised.

The investigation has been carried out by an independent, internationally composed Panel supported by an independent secretariat. The Panel has performed the investigation in accordance with the Terms of Reference and the process plan which was established as an appendix to the Terms of Reference (see annexes 2.1.1 and 2.1.2). The Panel finalized the investigation in summer 2012.

Before submitting the final investigation report to the University of Copenhagen 23 July 2012, the Panel had submitted a draft report to Milena Penkowa for commenting and received a statement from Dr. Penkowa with her comments. The Panel's concluding comments to Dr. Penkowa's statement are presented in section 1.2.

A summary of the Panel's completed investigation, including its assessments, recommendations and overall conclusions, is presented in section 1.3.

Chapter 2 describes the background for and purpose of the investigation as laid down in the Terms of Reference. In addition, the chapter briefly presents the Panel. Finally chapter 2 specifies the process and approach applied by the Panel in the investigation.

Chapter 3 specifies the information and documentation obtained by the Panel for its examination of the research of Milena Penkowa.

Chapter 4 presents the Panel's assessments and recommendations, including its overall conclusions concerning the research of Milena Penkowa.

The report is accompanied by several annexes, the list of which is indicated together with the list of contents on the first pages of the report.

1.2 The Panel's comments to the statement of Milena Penkowa concerning the investigation

The Panel mailed its draft report to Milena Penkowa 8 June 2012 for her commenting. Dr. Penkowa's statement with her comments to the investigation, received by the Panel 11 July, is attached as annex 1.1.

The Panel has the following four concluding comments in relation to Dr. Penkowa's statement. (The Panel's comments to Dr. Penkowa's statement are further specified in annex 1.3.):

1. Renouncement of suspicion of scientific dishonesty of Dr. Penkowa for one publication

The Panel accepts Milena Penkowa's comment (annex 1.1. p.1) regarding the paper Asmussen et al., J Neurosci Res. 2009[1], (numbered as A69 in the investigation report), that Dr. Penkowa has "*not personally performed these gels.*" i.e. two gels (figure 6a and 6b in the paper) which in the view of the Panel shows strikingly similar banding patterns including "marker artefacts". Since Dr. Penkowa has not participated particularly in this part of the research behind the paper, we have renounced our suspicion of potentially intentional scientific dishonesty of Dr. Penkowa for this paper.

Besides renouncing our suspicion of scientific dishonesty of Dr. Penkowa as regards this paper, the Panel has not found convincing argumentation from Dr. Penkowa for changing anything else in the investigation report.

2. The Panel's investigation is not a formal legal investigation

The Panel has noted that Dr. Penkowa states that (annex 1.1 p. 15, last sentences):
"The Panel's conclusions are not based upon evidence. Accordingly, the Panel has not addressed general legal principles of "burden-of-proof", although they are in force. The Panel is encouraged to address this matter before drawing any conclusions. All in all, the foundation for the Panel's work and even more so their conclusions are insufficient and worthless."

In relation to the above comment of Dr. Penkowa, the Panel wishes to emphasise that, in accordance with our Terms of Reference (annex 2.1.1), our investigation is not a formal legal account for proving or disproving scientific dishonesty of Milena Penkowa, and our task has not been to decide on the question of scientific dishonesty of Dr. Penkowa. On the contrary, our task has been to assess whether scientific dishonesty of Dr. Penkowa may be suspected and, if so, demonstrate our grounds for raising such suspicion.

[1] Asmussen JW, Von Sperling ML, Penkowa M.: Intraneuronal signaling pathways of metallothionein. J Neurosci Res. 2009 Oct;87(13):2926-36.

We thus agree with Dr. Penkowa that we have not, in a legal context, proven the suspicions of scientific dishonesty raised in our investigation report. In fact, we do not consider it possible in the framework of our investigation to have applied general legal principles of "burden-of-proof" for our suspicions about scientific dishonesty of Dr. Penkowa.

However, we conclude that we have found legitimate grounds, and documented these to a sufficient extent, for raising the suspicions of scientific dishonesty indicated in section 4.4 of the report and summarised in section 1.3.

3. The Panel's access to material

In addition the Panel has noted that Dr. Penkowa states that (annex 1.1 p. 15):
"It remains a fact that the Panel was not provided with decent working conditions. Accordingly, the contents of the report are based upon assumptions, guessing and uncertainty as to what sections and tissues belong to which project, not to mention which publication. Even worse, the Panel has not been able to get access to all relevant material, since substantial amounts of evidence still remain to be registered by the University."

We have not been able to prove the connections between the primary material found and analysed by us and the publications for which we have raised suspicion of scientific dishonesty of Dr. Penkowa. As indicated further above it has not been the intention of the investigation that the Panel should provide such proof.

However, for a number of the papers for which we raise suspicion of scientific dishonesty in the report, we have shown that the analysed material is connected with the papers with some probability. We do not find adequate basis for determining the exact size of this probability, only that we find it sufficient for assessing that the analyses of the primary material supports, or does not abolish, our grounds for suspecting dishonesty.

Concerning whether we have had access to the complete material from Dr. Penkowa's lab and office, we have noted the statements of Dr. Penkowa about the incompleteness of the archive. Similarly we have noted the statements of the University of Copenhagen regarding this issue. Finally we have indeed noted that the University has found further material, including the minus 80 degrees freezer, as late as in April-May, and we cannot exclude that additional material may exist which has not yet been brought to the archive.

However it is not within the framework of our investigation to make any decision or judgement as to whether the archive holds the complete set of items from Dr. Penkowa's lab and office as of the time when she left them, and/or whether the lack of structure of the archive reflects a lack of structure in Dr. Penkowa's previous lab and office. In the framework of our investigation, we find the material found and analysed by us to be sufficient documentation for the suspicions of scientific dishonesty raised in our report, regardless of

whether the archive has been complete or not, and of whether we have found all existing material connected to the scientific papers for which we have raised suspicion of dishonesty.

Please also note in this connection that for some papers we have concluded that we have not found grounds for raising suspicion of scientific dishonesty because the obtained documentation has been too insufficient to validate or invalidate the research and results in these papers, cf. section 4.4, page 44.

Furthermore we can add, as also described in the report and in annex 3.2.3.2, that we have inspected all freezers in the archive found by the University before May 2012. Furthermore, on 16 July 2012, the Secretariat has inspected the photos and written material found in April-May 2012 after the finding of the minus 80 degrees freezer. Based on the report on the Danish Committees on Scientific Dishonesty's visit to the archive 7 May 2012, sent to us by Dr. Penkowa 11 July 2012 (annex 1.2), we have specifically asked the University (11 July 2012) whether any further freezers or other material have been found from 1 May 2012 and forward. The University informed us that no further freezers or material have been found.

Thus, and in view of that the Panel's task has not been to apply general legal principles of "burden-of-proof" in our investigation, we find that our working conditions and access to relevant material have been satisfactory and sufficient for our drawing of the conclusions indicated in chapter 4 and summarised in section 1.3 of our report.

4. Participation and input from "both sides"

Finally the Panel notes that Dr. Penkowa states that (annex 1.1 p. 15):
"..the Panel's meeting in Copenhagen lacked participation and inputs from both sides – i.e. my most important collaborators and co-workers were not present nor were they allowed to submit a written report as in the case of Bente Klarlund."

The Panel disagrees with the above comment of Dr. Penkowa. As described in the report's section 3.3, we had in total seven meetings with different key-persons in relation to our investigation. Besides our meeting with Dr. Penkowa, two of the other meetings were with key-persons with whom Dr. Penkowa had requested us to meet.

Furthermore, any involved person has been free to submit written statements or reports – the Panel has taken all such received documents into consideration in the investigation, to the extent that they have been related to investigation (and written in English). The thus received documents include some reports which have been submitted on basis of inquiries from the Panel concerning specific scientific publications. For example, the Panel had invited Bente Klarlund Pedersen to a meeting, because we wanted to inquire specifically about some papers of which she was a co-author, and which we had selected for further investigation. As Dr. Pedersen was hindered in participating in a meeting on the possible dates we instead asked her to respond to our questions in a written statement. Similarly, we have obtained written information and documentation from Agnete Larsen, at whom Dr.

Penkowa has pointed as one of her most important collaborators, and to whom we had, earlier on, inquired about three specific papers.

Besides the survey conducted among co-authors in autumn 2011, the Panel has invited written statements only to the extent that we have had questions or inquiries. But had Dr. Penkowa wanted any statement from any collaborator she had been free to initiate this, and the Panel would have included the information in our investigation.

1.3 Summary of the Panel's investigation

The approach and process of the investigation

In accordance with the Terms of Reference, the task of the Panel has been to investigate the scientific output of Dr. Milena Penkowa regarding suspicion of scientific dishonesty. The investigation has thus comprised all scientific papers co-authored by Dr. Penkowa and published before the start of the investigation, with exception of publications which were already under investigation by the Police or by the Danish Committees on Scientific Dishonesty (DCSD).

Among the publications are several book chapters, reviews, abstracts, conference proceedings and announcements of retractions. We have found these types of papers not relevant for further investigation, as the research addressed in them is more thoroughly presented in the primary scientific papers.

Each of the thus remaining published articles (n=79) were evaluated in detail by the Panel. Annex 2.3.6 provides an overview of the published papers. Table 1 lists the 79 papers evaluated by the Panel, table 2 lists the 6 papers that have been reported to Police or DCSD, while table 3 lists the 23 book chapters, reviews etc.

For each paper we obtained written information on the roles of the co-authors and of Dr. Penkowa regarding the research presented in the article. In this way we identified manuscripts, in which Dr. Penkowa had not conducted the experiments or other research. These manuscripts were excluded from further investigation, as the task of the Panel has been to exclusively investigate the research of Dr. Penkowa.

After detailed reading of the remaining publications, the Panel selected 26 publications, which contained aspects that warranted more detailed investigation. These aspects included:

a) Inconsistencies between the described methods and the results or between the results, described in the text, and the respective photographic images,
b) unusual patterns of antigen expression, shown by immunocytochemistry,

c) questions regarding quantitative data, and
d) questions concerning documentation for animals used for the experiments.

For these papers, original slides and written documentation that with some probability could be associated with the identified papers were found in the archive, which contain the content of Dr. Penkowa's laboratory and office, and obtained from other sources (Co-authors of Dr. Penkowa, the Faculty of Health Sciences and more).

In addition the Panel obtained, in general, information and documentation for the animal experiments conducted by Dr. Penkowa, from the archive and from the Faculty of Health Sciences, co-authors and more.

The material, which was found, was analyzed in detail during the site visit of the Panel at the Panum Institute on 11-13 April 2012. Supplementary information was obtained at the Panel's meetings on 12 April 2012 with Dr. Penkowa, selected collaboration partners and representatives from the Faculty of Health Sciences; and further written documentation was obtained and examined after these meetings.

After having analysed all the obtained material and information, the Panel decided on its assessments and conclusions and elaborated its report on the investigation. The draft report was mailed to Milena Penkowa 8 June 2012 for her possible commenting on the report not later than 9 July, and the Panel mailed its final report to University of Copenhagen 23 July 2012.

Limitations of the investigation

In this investigation the Panel was confronted with a comprehensive task, since the topic covered more than ten years of scientific activity, 102 scientific publications and an enormous amount of original materials and documents, stored in the archive. For this reason the Panel had to concentrate on specific aspects and to focus on pre-selected examples of scientific papers (see above).

In addition, identification of specific material in the archive was very difficult and in some instances impossible, because the archive is unstructured and with only an incomplete index, the found folder "Key to Animals", for linking the written documentation and the primary samples with the experiments described in the papers.

Furthermore, the exact annotation of sections to individual animals of individual experiments was only partly possible, and we therefore chose in addition a different strategy for evaluation. We analyzed the immunocytochemical staining patterns for individual markers in a large amount of samples from different experiments and determined, whether the quality of the staining in general was sufficient to draw the conclusions reported in the publications.

Regarding animal experiments we encountered similar problems. In some cases it turned out difficult to match animal experiments from Dr. Penkowa's laboratory with the reports documented in the animal journals of Dr. Penkowa.

Assessments and Observations

The Panel was impressed by the amount of material, present in the form of embedded tissue blocks and stained tissue sections in the archive of Dr. Penkowa's laboratory. Thus, an enormous amount of work and effort has been invested into scientific activities by her and her team over the decade whence she has been employed at the University of Copenhagen. This view was further supported by the interviews with collaboration partners on 12 April 2012, in which Dr. Penkowa was described as a very hard working and highly motivated young scientist, who was also able to create a positive and productive environment for her team. The interviews further revealed that Dr. Penkowa was highly esteemed as a supportive and competent collaborator, who also was easy to motivate for new cooperative projects.

When we analyzed experiments done in collaboration, where Dr. Penkowa's role was essentially restricted to pathological analysis, we found no reason to doubt that the material, which was sent to Dr. Penkowa's laboratory from outside, was properly embedded and archived and respective sections and histological or immunocytochemical stains were performed, as outlined in the respective papers. Findings, reported in the papers, could be verified in many instances by analyzing the respective slides, and the photographic documentation in the papers reflected what was seen in the original slides. Furthermore, publications, which were performed in collaboration with other groups and where the actual data were gathered by students from other laboratories under Dr. Penkowa's supervision, did not raise suspicion, and this impression was also confirmed in interviews with co-authors.

Potential problems, however, were identified, when the published papers, in which the data were predominantly generated and interpreted by Dr. Penkowa, were analyzed in detail in relation to the material found in the archive. These problems were originally detected in the analysis of the 26 specific publications, which had been selected by the Panel in the course of the strategy, outlined above, and mainly in the papers published in the years 1999 to 2005. However, problems were also detected for papers published later. In addition, during the Panel's further studies, problems were identified in some of the papers which the Panel had not selected in the first round. The findings include the following aspects:

a) Problems related to the quality control of immunohistochemistry of cytokines, growth factors and markers for oxidative damage,

b) potential problems regarding the validity of published quantitative data,

c) discrepancies between animal numbers in the publications and actually documented experiments, and

d) inconsistencies regarding photographic documentation, including discrepancies between published images and changes seen in the actual slides.

Findings in relation to the Terms of Reference

The Terms of Reference specifically have asked to analyze Dr. Penkowa's publications regarding suspicion of scientific dishonesty. Obviously it is difficult to draw the line between unintentional errors and intentional falsification. However, the Panel suspects potentially intentional misconduct of Dr. Penkowa for several of the 26 selected papers. In addition, on basis of the Panel's examination of the obtained documentation, the Panel has found grounds for suspicion of potentially intentional dishonesty of Dr. Penkowa for several of the other 53 papers.

In total the Panel has found grounds for suspicion of potentially intentional dishonesty of Dr. Pankowa in the following 15 papers (indicated here by appendix numbers – see titles and other bibliographic data in annex 2.3.6):

A3, A5, A11, A13, A57, A65, A67, A76, A81, A84, A104, A108, A136, A138 and A140.

For these papers the Panel sees suspicion of potentially intentional misconduct of Dr. Penkowa in the following areas:

a) Publication of animal experiments, which (at least regarding animal numbers) may have not been performed as published. This involves publications A108 and 140. These two papers are based on the same animal experiments as the paper A102 which has been reported to the Police and which is not included in the Panel's investigation. The outcome of the Police investigation will thus apply to A108 and A140 also, and the Panel therefore decided to not assess these two papers any further or examine the found materials related to them.

b) Publication of immunocytochemical control experiments, which may not have been performed as described in the publication. This involves the following papers: A3, A11, A65, A76 and A81.

c) Publication of micrographs, which may not be derived from the original material of the respective experiment (A5, A13 and A104), or which may have been edited to strongly enhance a difference in staining intensity, which is hardly visible in original sections (A84). Whether there are additional original slides, which show the documented findings cannot be definitely excluded.

d) Reporting of quantitative data, which have little or no basis on the facts seen in the original slides (A3, A5, A11, A13, A57, A65, A67, A81, A104, A136 and A138). It cannot be completely excluded that there are still further slides, which were not available to the Panel but represent the basis for these quantitative analyses. This is, however, unlikely, since the Panel had access to a very large number of slides from the respective experiments, clearly labeled for immunocytochemistry for the respective antigens.

Assessment forms reporting on the Panel's detailed findings on each of those papers are included in annex 4.1.1.

After having examined the obtained documentation, the Panel has not found grounds for raising suspicion of scientific dishonesty of Dr. Penkowa for the remaining 64 papers. These papers include a number of those 26 papers which were first identified by the Panel for further investigation. The assessment forms reporting on the Panel's findings on each of the 64 papers are included in annex 4.1.2.

The institutional framework for Dr. Penkowa's research

In terms of the institutional framework for Dr. Penkowa's research at the University of Copenhagen, the Panel commends the implementation of procedures for quality control of the work of Dr. Penkowa in the Department for Neuroscience and Pharmacology in the last 1-2 years before she left the University.

However, we find that such quality control measures should have been implemented several years earlier. In particular we find that in her early Post Doc years Dr. Penkowa did not receive sufficient guidance and supervision, compared to international standards. The early post-doc position is one of the most critical periods in the career development of a young scientist. The solitary and independent position of Dr. Penkowa in her early Post Doc years, without proper coaching or quality control, together with her high level of ambition, may have contributed to the suspected flaws in her research, pointed out by the Panel in the report.

We have observed that the Faculty of Health Sciences has not had any formal rules on good scientific practice or on mentoring of young scientists, and we find this a part of the cause for the insufficient quality control of Dr. Penkowa's research for a number of years.

The Panel thus concludes that the suspected scientific dishonesty of Dr. Penkowa may have been precluded several years earlier than is the case, if the University of Copenhagen had had formal rules on good scientific practice or on mentoring of young scientists. The Panel takes the liberty to suggest some measures, which may in the future prevent such a situation:

1) Although they are not a granted remedy, formal rules of good scientific practice may help to guide young scientists in particular in their early career stages.

2) In addition, we find that ways should be found to grant supportive supervision to young scientists, while allowing the scientist to develop into an independent researcher.

3) Overall the system of research evaluation at the University of Copenhagen may rely too much on quantitative outcome measures rather than on actual quality. More weight could be placed on the extent of grant funding from institutions with international peer review as an additional quality control instrument. International evaluation of the research track at critical steps of career development would also be helpful.

2. Purpose and process of the investigation

This chapter explains the background for and purpose of the independent investigation into the research of Milena Penkowa, by presenting extracts from the Terms of Reference (section 2.1) for the investigation. In addition, the independent Panel who has completed the investigation is presented (section 2.2). Finally the process and approach applied by the Panel in the investigation are described (section 2.3).

2.1 Background for and purpose of the investigation

Background

The independent investigation into the research of Milena Penkowa was initiated by the University of Copenhagen in summer 2011. According to the Terms of Reference (annex 2.1.1), the University found it necessary to organise the investigation due to doubts about the honesty of the scientific work conducted by Milena Penkowa. The doubts were based on suspicions of scientific dishonesty in Milena Penkowa's research presented in specific publications, which the University had reported in 2010 and 2011 to the Danish Committees on Scientific Dishonesty (DCSD), and in one case in 2011 to the Copenhagen Police.

The Terms of Reference thus say that: "The well-founded suspicion underlying the above-mentioned reports [to Police and DCSD] may raise doubts about the honesty of other scientific work conducted by Milena Penkowa. Consequently, the University of Copenhagen finds it necessary to organise an investigation into the honesty of the research forming the basis of all Milena Penkowa's published scientific articles." The scientific articles reported to the Copenhagen Police or DCSD before the start of the investigation are not included in the Panel's investigation.

Purpose

The investigation has several purposes according to the Terms of Reference, namely:

"The investigation will be conducted primarily to secure the sustained confidence in the University's research and its researchers, but also out of regard for Milena Penkowa's co-authors, who may feel that their own research is subject to suspicion."

and:

"The investigation must clarify whether – and, if so, to what extent – questions about the scientific honesty of Milena Penkowa's additional research can be raised ... The panel shall not decide on the question of scientific dishonesty, but provide the factual basis for a statement about that question to the University of Copenhagen. Following the investigation, the University will decide whether there are grounds for the University to report more of Milena Penkowa's research to DCSD in order to obtain DCSD's decision as to whether scientific dishonesty is present."

The Terms of Reference also state that "the investigation will focus exclusively on Milena Penkowa's scientific production. Consequently, Milena Penkowa's co-authors of published articles are not subjects of the investigation."

In accordance with the Terms of Reference, the Panel has used the same definition of scientific dishonesty as the DCSD. These criteria are indicated in § 2 in the executive order on DSCD[2], which defines scientific dishonesty as:

"Scientific dishonesty shall mean: Falsification, fabrication, plagiarism and other serious violation of good scientific practice committed wilfully or grossly negligent on planning, performance or reporting of research results. Included hereunder are:
1) Undisclosed fabrication and construction of data or substitution with fictitious data.
2) Undisclosed selective or surreptitious discarding of a person's own undesired results.
3) Undisclosed unusual and misleading use of statistical methods.
4) Undisclosed biased or distorted interpretation of a person's own results and conclusions.
5) Plagiarizing of other persons' results or publications.
6) A false credit given to the author or authors, misrepresentation of title or workplace.
7) Submission of incorrect information about scientific qualifications."

Work process and time schedule

The process plan of the investigation (see annex 2.1.2) has laid down the overall time schedule and work process of the investigation.

As a basis for the investigation, copies of the published scientific articles, to which Milena Penkowa had contributed, were made available to the Panel by the University of Copenhagen. Annex 2.1.3 provides an overview of those papers. The basis for the Panel's investigation is thus 102 papers. The 6 articles reported to the Police or DCSD before the start of the investigation are also included in the overview, although they were not to be investigated by the Panel. All the papers have been given an "A-number" (appendix number), i.e. an ID code, for the operational expediency of the investigation.

[2] Executive order no. 306 of 20 April 2009 on the Danish Committees on Scientific Dishonesty (DCSD). English version: http://en.fi.dk/acts/executive-order-no.-668-of-28-june-2005-on-the-danish-commit/

The Terms of Reference also state that obtaining experimental material and other documentation is essential for the Panel to complete the assignment. The Panel must thus procure information and material etc. to the extent necessary in order to produce its statement to the University of Copenhagen on whether the honesty of Milena Penkowa's research can be questioned. Relevant information and materials etc. can be obtained from Milena Penkowa, her co-authors, the University or from other sources.

The investigation report

According to the Terms of Reference, the Panel's investigation report shall indicate whether – and potentially to what extent – it has not been possible to assess the honesty of Milena Penkowa's research, for example due to lack of access to documentation. In addition, the report must include the Panel's motivated conclusion on whether it finds a well-founded suspicion of scientific dishonesty as defined in the Terms of Reference – in one or more of the published scientific papers, to which Milena Penkowa has contributed with her research. If the panel finds such suspicion, the report must state which article(s), including the underlying research the suspicion concerns, and substantiate and document the suspicion.

Milena Penkowa must be given the opportunity to comment on a draft of the Panel's final report.

In addition to the investigation report, the University of Copenhagen must receive all additional relevant material, on which the Panel has based its conclusions.

The investigation report with appendices submitted to the University will be publicly accessible according to the regulations of the Danish Public Information Act. Similarly, material submitted by the University to the Panel will be accessible for the public in accordance with the right of access to documents provided for in the Danish Public Information Act.

Based on the investigation report, the University of Copenhagen will decide on the possible consequences, which the University wishes to effect, including whether there is reason to file additional reports concerning Milena Penkowa's research to DCSD.

2.2 The Investigation Panel

In agreement with the Ministry of Science, Technology and Innovation and on the basis of specific advice from the Danish Council for Independent Research (DFF), the University of Copenhagen appointed a panel of the following 5 internationally recognised experts within the relevant research areas to carry out the investigation:

- Professor Hans Lassmann, MD (Chairman), Centre for Brain Research, Division of Neuroimmunology, Medical University of Vienna, Austria
- Professor Anders Blomqvist, Department of Clinical and Experimental Medicine, Division of Cell Biology, Linköping University, Sweden
- Prof. Dr. Christine D. Dijkstra, Department of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, the Netherlands
- Professor Margaret M. Esiri, Department of Clinical Neurology (Neuropathology Department), University of Oxford, United Kingdom
- Professor Hartmut Wekerle, Max Planck Institute of Neurobiology, München, Germany.

The Panel's work has been supported by a secretariat constituted by:

- Professor Emeritus Lars Terenius, Karolinska Institutet, Stockholm, medical expert in the Secretariat
- Independent Consultant, M.Sc.Eng. Pia Jørnø, Copenhagen, Leader of the Secretariat.

As indicated in the Terms of Reference, the Panel and the Secretariat are not a part of the Danish public administration. Therefore, the Panel and the Secretariat are not covered by the Act on Access to Public Administration Files.

In addition, the Panel and the Secretariat are independent in relation to the University of Copenhagen, and the University is thus not in a position to give instructions to the Panel or the Secretariat.

The University of Copenhagen has made legal assistance available to the Panel during the investigation, by the legal experts[3]:

- Former President of the Danish Supreme Court Torben Melchior
- Judge at the High-Court of Western Denmark, former Academic Officer at the Parliamentary Ombudsman, Michael Thuesen.

Before initiating the investigation, the University of Copenhagen has ensured that the appointment of the members of the panel, the secretariat and the legal experts does not give rise to any conflicts of interest in relation to Milena Penkowa or the University of Copenhagen.

[3] The two legal experts are affiliated to the University of Copenhagen as a part of the University during the investigation, and they have both assisted the University in connection with the establishment of the investigation.

2.3 Process of the investigation

This section (2.3) describes the process and approach of the investigation, including the survey conducted among the co-authors of Milena Penkowa (including Dr. Penkowa), the Panel's examination of the scientific papers, the searches for background documentation for the research of Milena Penkowa and the Panel's meetings.

The information and documentation found during this process are presented in chapter 3.

2.3.1 Initiation of the investigation and survey among the co-authors (July – August 2011)

The investigation was initiated by introductory letters of 5 July 2011 from the University of Copenhagen to Milena Penkowa and to her co-authors, respectively (annex 2.3.1 and 2.3.2).

Following University of Copenhagen's introductory letters, the Secretariat to the Investigation Panel conducted a survey aimed at identifying Milena Penkowa's scientific work. In the survey, in the period 12 July – 1 August 2011, 530 questionnaires were distributed to 165 co-authors (including Dr. Penkowa) concerning the published scientific papers co-authored by Milena Penkowa. (Each author received a questionnaire for each paper he/she has co-authored with Dr. Penkowa). The questionnaires asked for information on Milena Penkowa's, respectively the co-authors', scientific contributions to the papers. The final deadline for responding to the questionnaires was 31 August 2011.

The Secretariat delivered the responses (including the received enclosures to the responses) from the authors, organised in an operational form, to the Panel by e-mail 27 September, and in hard copy 10 October. (A few questionnaires were sent, and responses received, later in the process of the investigation. These responses were e-mailed to the Panel.)

More specifics on the process of the survey are presented in annex 2.3.3. The results of the survey are described in chapter 3.

2.3.2 First Panel meeting (10-11 October 2011)

The Panel met in Copenhagen 10-11 October in order to become familiarised with its task and to plan in detail its work with the investigation.

The meeting was started with an introduction by the University of Copenhagen of the Terms of Reference including information on the background for the investigation and discussions between the Panel and University of Copenhagen on various aspects of the Panel's task. Annex 2.3.4 presents the minutes from the meeting with the University.

The rest of the Panel's meeting was Panel-internal. On the Panel-internal meeting, the Secretariat presented an overview of the scientific papers comprised by the

investigation, and of the co-authors of Milena Penkowa. In addition the Secretariat presented the result of the completed survey among the co-authors. At the last part of the meeting, the Panel discussed its task, determined its procedure and approved the process plan (annex 2.1.2) for completion of the investigation. Annex 2.3.5 contains the minutes from the Panel's meeting.

The published scientific papers comprised by the investigation

In accordance with the Terms of Reference the Panel decided, at its meeting 10-11 October 2011, to start its investigation with a study of the 102 scientific papers that have been included in the investigation. As indicated earlier, these comprise all papers co-authored by Milena Penkowa and published before the start of the investigation, i.e. before July 2011, except those 6 papers that have been reported to the Copenhagen Police or the Danish Committees on Scientific Dishonesty (DCSD) before July 2011.

At its October meeting, the Panel concluded that book chapters, reviews, abstracts, conference proceedings and announcements of retractions[4] would not be relevant for further investigation, as the research addressed in them is more thoroughly presented in the primary scientific papers. Among the 102 published papers, the Panel identified 23 papers of these types.

Thus, 79 papers remained for being evaluated by the Panel. Table 1 in annex 2.3.6 shows an overview of these papers.

Table 2 in the annex shows the 6 scientific papers that had been reported to the Danish Police or the Danish Committees on Scientific Dishonesty (DCSD) before July 2011.

Table 3 in the annex shows the 23 book chapters, reviews, abstracts, conference proceedings and announcements of retractions which the Panel decided not to investigate.

As mentioned in section 2.1, all the papers have been given an "A-number" (appendix number), i.e. an ID code, for the operational expediency of the investigation.

2.3.3 The Panel's analyses of the scientific papers comprised by the investigation

Following the Panel's meeting 10-11 October, the 79 published scientific papers comprised by the investigation were each evaluated in detail by members of the Panel together with the authors' questionnaire responses (and enclosures) obtained through the survey conducted in July-August 2011. With the aim of obtaining a complete knowledge of the

[4] The announcements of retractions (A306 and A307) concern retraction of two articles (A36 and A37) which had previously been reported to the Danish Committees on Scientific Dishonesty (DCSD) and which are not included in the Panel's investigation.

scientific articles published by Milena Penkowa, the Panel also studied the 6 papers reported to the Police or the DCSD.

In order to optimise the efficiency and effectiveness of the Panel's analyses of the papers, the Panel assigned the papers to its members in accordance with their fields of expertise.

For each of the 79 studied papers, the Panel filled in an assessment form, indicating whether no dishonesty was suspected for the paper or whether there was a need for further investigation before a possible suspicion of scientific dishonesty could be either rejected or confirmed. In the forms the Panel also indicated whether, and which, material should be procured for documenting the research described in the paper (e.g. primary samples, protocols on experiments, illustrations etc.). A copy of the assessment form is attached in annex 2.3.7.

The Panel's detailed studies of the scientific papers supplemented by the information from the questionnaire responses, resulting in the completed assessment forms, were concluded 31 January. The completed assessment forms are addressed in, and annexed to, chapter 4.

2.3.4 The Panel's identification of papers for which further background documentation should be obtained and analysed

On the basis of its detailed studies of the 79 scientific papers and the information provided by the co-authors (including Milena Penkowa) in the questionnaires, the Panel identified 23 publications, in which were found aspects that required further investigation. For these papers the Panel requested, in the assessment forms, specific background documentation (including lab protocols, primary materials, documentation on immunohistochemistry procedures and documentation for conducted animal experiments) for further examination.

Furthermore, the Panel selected 3 papers for which the Secretariat conducted an examination of the documentation for the animal experiments described in these papers.

For each of the other papers, i.e. papers for which the Panel did not find grounds for suspecting scientific dishonesty, as well as papers where Milena Penkowa's role in the research has been minor, an assessment form was completed indicating that no aspects were detected which raised suspicion of scientific dishonesty of Dr. Penkowa.

2.3.5 Collection of documentation for animal experiments, procedures for documenting research and more

Concurrent with the Panel's above-mentioned survey of the papers and the responses from the co-authors, the Secretariat worked on obtaining various written materials, in accordance

with the Panel's decisions on its approach and the process of the investigation. This material included documentation for the animal experiments described in the papers, rules for experiments and overall procedures for good scientific practice and information on the organisational placement of Milena Penkowa, including her responsibilities during the years of her employment at the University of Copenhagen, and more. Annex 2.3.8 provides more details on the types of documentation sought.

The Secretariat sought and obtained the documentation and information through several sources including: The Secretariat of SUND; the Department of Experimental Medicine which houses all the experimental animals at SUND; the Department of Neuroscience and Pharmacology (the department at which Milena Penkowa was employed before she left the University), Dyreforsøgstilsynet (the Danish Animal Experiments Inspectorate), the Danish Committees on Health Research Ethics and some of Dr. Penkowa's co-authors/collaboration partners.

In addition, and not least, the documentation was sought in the archive holding the items from Milena Penkowa's previous office and lab (also called *the MP archive* in this report). The searches in the MP archive were prepared through detailed studies of the catalogue in which all the items in the MP archive are listed. The visits to the MP archive took place 7 and 13 December 2011. In addition the Secretariat visited the archive 7-8 February, 20-21 March, 28 March and 20 April – these visits are described further below. During the visits, the Secretariat photo-copied various written material found in the archive. Both the visits and the photo-copying were conducted under supervision of Inge-Lise Damberg, Senior Adviser, SUND's Faculty Service, and all materials that were removed for photo-copying were replaced at the exact same locations in the archive immediately after the photo-copying.

The catalogue on the archive displays that the extensive written material and primary material in the MP archive are stored in an unstructured way. The visits to the archive have confirmed this picture, since the various items are stored in exactly the same order as registered in the catalogue.

According to SUND, all the materials in the MP archive have been stored, and registered in the catalogue, in exactly the same order as found in the office and lab of Milena Penkowa. According to a note with remarks by Dr. Penkowa, mailed to the Panel 6 April 2012 (see annex 2.3.9), the disorganisation of the archive is caused by visits of various parties in the archive, during which documentation has been removed and/or re-organised. The University has informed the Panel that the only materials which have been removed from the archive is the material confiscated by the Police in connection with their investigation of the matter reported by the University of Copenhagen in 2011, and that the Police had returned these materials before all material from Milena Penkowa's lab and office were moved to the archive 5 September 2011.

2.3.6 Searches for documentation for the papers selected by the Panel

After the Panel's completion of the assessment forms, the Secretariat visited the MP archive 8-9 February and 20, 21 and 28 March with the particular aim of searching for the background material that the Panel had requested in the assessment forms as documentation for the selected papers. In advance of the visit the Secretariat had made detailed preparations for the visit, including the visits to the archive in December 2011, detailed studies of the catalogue on the archive, and elaboration of lists with keywords on what to look for in the archive. In addition the Secretariat obtained information requested by the Panel for the selected papers directly from some of Milena Penkowa's co-authors.

Due to the unstructured archive it turned out to be more difficult and time-demanding than initially expected to identify the materials requested by the Panel, and some of the requested materials were not found.

In its search for the requested material, the Secretariat focused on the following search activities:

A. Search for the "keys" for the experiments presented in the papers selected by the Panel
During the Secretariat's studies of the catalogue on the archive and the visits in the archive in December 2011, the Secretariat concluded that the connections between the stored primary material and the experiments described in the scientific papers were to be found in the folder "Key to Animals" in room 11 in the MP archive. The "Key to Animals" folder contains sheets with descriptions of conducted experiments showing (some of) the connections between conducted experiments and the Keys (i.e. ID codes) that are indicated on the sample boxes. The Key to Animals folder contains keys and descriptions for animal experiments as well as experiments involving humans. Most of the Keys consist of 1-2 letters, e.g "V" or "HH".

On 8-9 February 2012, the Secretariat therefore completed a detailed examination of this red folder in order to find possible connections between the Keys (i.e. ID codes), with which the slide boxes are labelled, and the experiments (animal experiments, studies involving humans and immunohistochemistry experiments) that are presented in the papers selected by the Panel. In advance of the examination of the folder, the Secretariat had prepared an overview of the experiments presented in the selected papers, in order to identify the relevant keys as expediently as possible during the visit.

B. Identification and collection of possibly relevant slide boxes
Following the February visit in the archive, on the basis of the found keys which could be identified as being, with some probability, the ID codes/labels for slides from experiments presented in the selected papers, the secretariat identified several slide boxes labelled with these keys, by a detailed examination of the catalogue on the archive.

These boxes thus contain slides, which with some probability are the primary sample material behind experiments presented in the selected papers.

Subsequently, under supervision of and with assistance from Inge-Lise Damberg, Senior Adviser, SUND's Faculty Service, the Secretariat collected and packed the

identified slide boxes on 20, 21 and 28 March; and ahead of the Panel's assembly at Panum on 11-12 April the boxes were moved to the microscope room of the Panel under supervision of Inge-Lise Damberg and Steen Pedersen, Engineer's Assistant, Department of Neuroscience and Pharmacology. After the Panel's assembly, the boxes were moved back to the archive under supervision of Steen Ruben, Head of Security, SUND. Under supervision of Inge-Lise Damberg, the Secretariat replaced all the boxes in their original locations in the archive 11 May 2012.

C. Searches for written documentation and photos
Supplementary to the earlier searches among the written documentation in the MP archive, on 8-9 February the Secretariat examined an external hard disc for obtaining material such as experiment records, lab protocols, lab procedure instructions, photos and correspondence with the scientific journals on the selected papers. SUND has informed the Panel that the Faculty's IT department has copied all files from the computers and hard discs from Milena Penkowa's lab and office to this external hard disc.

D. Searches for procedure instructions and data sheets on antibodies
In addition the Secretariat searched several sources to find the requested documentation on specific procedures for stainings, cell counts etc. The sources include Milena Penkowa's enclosures to her questionnaire response received by the Secretariat in August 2011, the external hard-disc containing all files from Dr. Penkowa's computers and hard discs and the large archive boxes with several documents in the MP archive.

E. Searches for documentation directly from co-authors
Furthermore, from February to 10 April 2012, the Secretariat obtained further information from co-authors of Dr. Penkowa, including written documentation, photos and slides from experiments presented in some of the papers selected by the Panel.

F. Specific search for documentation for the animal experiments in 3 selected papers
Finally the Secretariat searched, in the MP archive and by contacting a co-author, for documentation for the animal experiments described in the 3 papers that the Panel had selected for particular examination of the animal experiments.

2.3.7 Second Panel meeting (11-13 April 2012)

The Panel met at the Panum Institute, at The Faculty of Health Sciences (SUND), 11-13 April 2012 and carried out the following tasks:

- Conducted microscopy analyses of the obtained primary material (slides) supplemented by studies of the obtained written documentation and photos.
- Visited the MP archive. This included inspection of the folder "Key to animals" and of frozen samples which had been pre-identified by the secretariat as "maybe-associated" with some of the selected papers. Finally the Panel inspected a -80 freezer, the finding of which the Panel had been informed about on 3 April 2012.

- Met with and interviewed selected key-persons for obtaining supplementary information. The key-persons included Milena Penkowa, selected co-workers and co-authors of Dr. Penkowa, the Dean of SUND and Heads of the departments in which Dr. Penkowa had been employed.
- Discussed the Panel's observations, assessments and general conclusions, based on the obtained documentation and information.

The minutes from the second Panel on 11-13 April 2012 are attached as annex 2.3.10.

2.3.8 Additional searches for documentation

After the meeting 11-13 April 2012, the Panel completed a follow up concerning the contents of the "-80 freezer" found by SUND shortly before the meeting. This follow up was done by a detailed study of a catalogue, received from SUND 10 May 2012, which specifies the content of the freezers in the archive, supplemented by additional information from the Faculty.

In addition, based on information from Milena Penkowa during the meeting on 12 April, and after further study of the catalogue on the whole MP archive, the Secretariat went again to the archive on 20 April to obtain further documentation, including procedure protocols, data sheets on antibodies and receipts for the purchase of experimental animals.

Finally the Secretariat has obtained information from SUND concerning two backup servers, about which Milena Penkowa informed the Panel during the meeting 12 April 2012. Dr. Penkowa conveyed the URL addresses of these two servers and told that the first was obtained in 2005 while the second was obtained in approximately 2006. According to SUND the first server worked about two years, after when it broke down and became replaced by the second server. The second server was still in the lab of Dr. Penkowa when she left the University in 2010.

The Panel thus assumes that the files on the first server have not been available since it broke down, while the files on the second server are included in the external hard disc, which contains all files from the computers and hard discs from Dr. Penkowa's lab and office, and which the Secretariat examined 8-9 February 20 12

2.3.9 Elaboration of the report

After having obtained and analysed the additional material and information, the Panel prepared its report to the University of Copenhagen on the conducted investigation and the Panel's assessments and conclusions. The draft report was mailed to Milena Penkowa 8 June 2012 for her possible commenting not later than 9 July. On 9 July the Panel accepted a

postponement of this deadline until 11 July, requested by the attorney of Dr. Penkowa 7 July (Saturday).

The Panel mailed its final report to University of Copenhagen as well as to Dr. Penkowa 23 July 2012. The statement with comments and a further document from Dr. Penkowa, received 11 July, have been annexed as annexes 1.1 and 1.2 to the final report. The Panel has presented its concluding comments to Dr. Penkowa's statement in section 1.2 in the final report, and specified its comments to Dr. Penkowa's statement in annex 1.3.

3. Information and documentation obtained

This chapter (3) describes the documentation obtained, including: the result of the survey conducted among the co-authors of Milena Penkowa, including Dr. Penkowa (section 3.1); the result of the Panel's examination of the scientific papers, the documentation found for the papers selected by the Panel and other/further documentation found (section 3.2); and the outcome of the Panel's meetings with key persons on 12 April 2012 (section 3.3).

3.1 Result of the questionnaire survey

As indicated in section 2.3.1, questionnaires were mailed in July-August 2011 to co-authors of Milena Penkowa (including Dr. Penkowa) concerning the scientific papers co-authored by Dr. Penkowa. The overall purpose of this survey was to obtain the best possible basis for the Panel's future examination of Milena Penkowa's research by obtaining the best possible identification of the research conducted by her. The questionnaires thus asked for information on Milena Penkowa's, respectively the co-authors', scientific contributions to the papers.

Each author received a questionnaire for each co-authorship, i.e. for each paper he/she has co-authored with Dr. Penkowa. In total 530 questionnaires were distributed to 165 co-authors (incl. Dr. Penkowa).

124 of these co-authors (incl. Dr. Penkowa) have answered in total 472 of these questionnaires. The Secretariat has thus received responses to 89 % of the distributed questionnaires[5]. There is a response from one or more of Milena Penkowa's co-authors for all papers except for two papers (A131 and A302) and except for those few papers of which Dr. Penkowa is sole author.

The result of the survey together with the studied scientific papers (full text) have been a valuable basis for the Panel's assessments and for its identification of papers for which further documentation and information should be collected (e.g. lab reports, primary samples, illustrations etc.).

More specifics on the result of the survey are presented in annex 3.1.1 and the questionnaire responses with enclosures received from co-authors are collected in annex 3.1.2.1 and annex 3.1.2.2 (four files with enclosures).

[5] It has not been possible to distribute questionnaires to *all* the co-authors, as it has not been possible to find contact data for all co-authors. If related to *all* co-authorships of *all* the co-authors, the response rate is 75 %.

3.2 Documentation obtained

3.2.1 The papers selected by the Panel

As mentioned in section 2.3.4, the Panel identified 26 papers for which it requested specific documentation for its further examination. The bibliographic data for these 26 papers are listed in table 1 below. For all the other papers comprised by the investigation, the Panel requested no further documentation.

Table 1. Bibliographic data for the papers selected by the Panel

A.no [1)]	Title of paper and other bibliographic data
5	Altered inflammatory response and increased neurodegeneration in metallothionein I+II deficient mice during experimental autoimmune encephalomyelitis. Penkowa M, Espejo C, Martínez-Cáceres EM, Poulsen CB, Montalban X, Hidalgo J. J Neuroimmunol. 2001 Oct 1;119(2):248-60.
8	Associations between insulin resistance and TNF-alpha in plasma, skeletal muscle and adipose tissue in humans with and without type 2 diabetes. [2)] Plomgaard P, Nielsen AR, Fischer CP, Mortensen OH, Broholm C, Penkowa M, Krogh-Madsen R, Erikstrup C, Lindegaard B, Petersen AM, Taudorf S, Pedersen BK. Diabetologia. 2007 Dec;50(12):2562-71. Epub 2007 Oct 10.
13	Astrocyte-targeted expression of interleukin-6 protects the central nervous system during neuroglial degeneration induced by 6-aminonicotinamide. Penkowa M, Camats J, Hadberg H, Quintana A, Rojas S, Giralt M, Molinero A, Campbell IL, Hidalgo J. J Neurosci Res. 2003 Aug 15;73(4):481-96.
16	Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. [2)] Matthews VB, Aström MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, Akerström T, Yfanti C, Broholm C, Mortensen OH, Penkowa M, Hojman P, Zankari A, Watt MJ, Bruunsgaard H, Pedersen BK, Febbraio MA. Diabetologia. 2009 Jul;52(7):1409-18. Epub 2009 Apr 22.
33	Elevated levels of IL-18 in plasma and skeletal muscle in chronic obstructive pulmonary disease. [2)] Petersen AM, Penkowa M, Iversen M, Frydelund-Larsen L, Andersen JL, Mortensen J, Lange P, Pedersen BK. Lung. 2007 May-Jun;185(3):161-71. Epub 2007 Apr 10.
38	Exercise induces interleukin-8 receptor (CXCR2) expression in human skeletal muscle. [2)] Frydelund-Larsen L, Penkowa M, Akerstrom T, Zankari A, Nielsen S, Pedersen BK. Exp Physiol. 2007 Jan;92(1):233-40. Epub 2006 Oct 9.
40	Fiber type specific expression of TNF-alpha, IL-6 and IL-18 in human skeletal muscles. [2)] Plomgaard P, Penkowa M, Pedersen BK. Exerc Immunol Rev. 2005;11:53-63.
56	Impaired inflammatory response to glial cell death in genetically metallothionein-I- and -II-deficient mice. Penkowa M, Giralt M, Moos T, Thomsen PS, Hernández J, Hidalgo J. Exp Neurol. 1999 Mar;156(1):149-64.

63	Increased demyelination and axonal damage in metallothionein I+II-deficient mice during experimental autoimmune encephalomyelitis. Penkowa M, Espejo C, Martínez-Cáceres EM, Montalban X, Hidalgo J. Cell Mol Life Sci. 2003 Jan;60(1):185-97.
69	Intraneuronal signaling pathways of metallothionein. Asmussen JW, Von Sperling ML, Penkowa M. J Neurosci Res. 2009 Oct;87(13):2926-36.
73	Metallic gold reduces TNFalpha expression, oxidative DNA damage and pro-apoptotic signals after experimental brain injury. Pedersen MO, Larsen A, Pedersen DS, Stoltenberg M, Penkowa M. Brain Res. 2009 May 19;1271:103-13. Epub 2009 Mar 25.
84	Metallothionein-mediated antioxidant defense system and its response to exercise training are impaired in human type 2 diabetes. Scheede-Bergdahl C, Penkowa M, Hidalgo J, Olsen DB, Schjerling P, Prats C, Boushel R, Dela F. Diabetes. 2005 Nov;54(11):3089-94.
90	Metallothionein as a useful marker in Hodgkin lymphoma subclassification. Penkowa M, Sørensen BL, Nielsen SL, Hansen PB. Leuk Lymphoma. 2009 Feb;50(2):200-10.
96	Metallothionein expression in the central nervous system of multiple sclerosis patients. Penkowa M, Espejo C, Ortega-Aznar A, Hidalgo J, Montalban X, Martínez Cáceres EM. Cell Mol Life Sci. 2003 Jun;60(6):1258-66.
104	Metallothionein prevents neurodegeneration and central nervous system cell death after treatment with gliotoxin 6-aminonicotinamide. Penkowa M, Quintana A, Carrasco J, Giralt M, Molinero A, Hidalgo J. J Neurosci Res. 2004 Jul 1;77(1):35-53.
106	Metallothionein reduces central nervous system inflammation, neurodegeneration, and cell death following kainic acid-induced epileptic seizures. Penkowa M, Florit S, Giralt M, Quintana A, Molinero A, Carrasco J, Hidalgo J. J Neurosci Res. 2005 Feb 15;79(4):522-34.
108	Metallothionein treatment reduces proinflammatory cytokines IL-6 and TNF-alpha and apoptotic cell death during experimental autoimmune encephalomyelitis (EAE). Penkowa M, Hidalgo J. Exp Neurol. 2001 Jul;170(1):1-14.
124	Role of metallothionein-III following central nervous system damage. Carrasco J, Penkowa M, Giralt M, Camats J, Molinero A, Campbell IL, Palmiter RD, Hidalgo J. Neurobiol Dis. 2003 Jun;13(1):22-36.
136	Time-course expression of CNS inflammatory, neurodegenerative tissue repair markers and metallothioneins during experimental autoimmune encephalomyelitis. Espejo C, Penkowa M, Demestre M, Montalban X, Martínez-Cáceres EM. Neuroscience. 2005;132(4):1135-49.
138	Treatment with anti-interferon-gamma monoclonal antibodies modifies experimental autoimmune encephalomyelitis in interferon-gamma receptor knockout mice. Espejo C, Penkowa M, Sáez-Torres I, Xaus J, Celada A, Montalban X, Martínez-Cáceres EM. Exp Neurol. 2001 Dec;172(2):460-8.
140	Treatment with metallothionein prevents demyelination and axonal damage and increases oligodendrocyte precursors and tissue repair during experimental autoimmune encephalomyelitis. Penkowa M, Hidalgo J. J Neurosci Res. 2003 Jun 1;72(5):574-86.

143	Zinc or copper deficiency-induced impaired inflammatory response to brain trauma may be caused by the concomitant metallothionein changes. Penkowa M, Giralt M, Thomsen PS, Carrasco J, Hidalgo J. J Neurotrauma. 2001 Apr;18(4):447-63.
207	Metallothionein-I + II and receptor megalin are altered in relation to oxidative stress in cerebral lymphomas. Pedersen MØ, Hansen PB, Nielsen SL, Penkowa M. Leuk Lymphoma. 2010 Feb;51(2):314-28.
208	Bio-released gold ions modulate expression of neuroprotective and hematopoietic factors after brain injury. Pedersen MØ, Larsen A, Stoltenberg M, Penkowa M. Brain Res. 2010 Jan 11;1307:1-13. Epub 2009 Oct 17.
211	Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. [2)] Nielsen AR, Mounier R, Plomgaard P, Mortensen OH, Penkowa M, Speerschneider T, Pilegaard H, Pedersen BK. J Physiol. 2007 Oct 1;584(Pt 1):305-12. Epub 2007 Aug 9.
302	Metallic gold treatment reduces proliferation of inflammatory cells, increases expression of VEGF and FGF, and stimulates cell proliferation in the subventricular zone following experimental traumatic brain injury. Pedersen MØ, Larsen A, Pedersen DS, Stoltenberg M, Penkova M. Histol Histopathol. 2009. May;24(5):573-86.

[1)] A.no = appendix no. = the Panel's "working-number" of the paper.

[2)] The papers marked with [2)] above, i.e. A8, A16, A33, A38, A40 and A211, which are all included in the Panel's investigation, and which are among the papers selected by the Panel, have been reported to University of Copenhagen and DCSD July/August 2011 by Prof. Galbo and subsequently reported to DCSD by Prof. Klarlund Pedersen.

3.2.2 Found documentation behind the papers selected by the Panel Members

For the 26 papers selected by the Panel, the following documentation was found on the basis of the search activities described in section 2.3.6:

Ad A. Found keys

In the folder "Key to Animals" in the MP archive, the Secretariat, on 8-9 February 2012, found several possible connections between the keys (i.e. ID codes), with which the slide boxes are labelled, and the experiments (animal experiments, experiments involving humans and immunohistochemistry experiments), that are described/presented in the papers selected by the Panel. Most of the keys consist of 1-2 letters, e.g "V" or "HH".

Annex 3.2.2 shows the keys that were found to be associated, with some probability, with the experiments described in the selected papers. Thus, the annex also shows the probable associations between each found key and the specific scientific paper(s).

The sheets, which were found in the Key to Animals folder, and which, key by key, contain indications of experiments similar to those that are presented in the selected

papers, are scanned into files – one for each selected paper – in annex 3.2.4.1. Please note that the found key sheets for two of the selected papers (A90 and A207) are not scanned into the annex files, as these sheets contain several CPR numbers of patients.

The Secretariat did not succeed with finding any keys that could be associated with the papers A56, A69 and A84. (For A84, some slides were obtained by a co-author, see "Ad E." further below).

The found "Key to Animals" folder is stored on a shelf in the MP archive room 11. In addition a copy of this folder is stored in a plastic cover in a large-box in the MP archive room 17.

During the meeting with Milena Penkowa on 12 April 2012, she explained that until March 2010 she had, in her office, 1-2 folders with keys identifying the connections between the primary material and the experiments conducted, and that this/these folder(s) is the most important item, containing the keys, for finding the connections between the slides and the experiments, including information on both animal and human tissue. She told further that the folder(s) contains sheets for the different experiments, ID'ed with letters (starting with A, B, etc. and later on AA, AB etc.) in order to distinguish the different experiments from each other. On the sheets are also indicated the exact numbers of animals and the experiments conducted on them. As far as Milena Penkowa remembers, the folder(s) was labelled something like "dyrebog" ("animal book"), was either red or pink, and contains information on both animal and human tissue.

The Panel concludes that the folder "Key to Animals" identified in the archive by the Secretariat in December 2011 with high probability is the folder(s) to which Dr. Penkowa refers for finding the connections between the samples with the experiments, due to the significant similarities between Dr. Penkowa's description of her "ID folder(s)" and the found folder.

The Panel notes, however, that the found folder "Key to Animals" is disorganised: Several of the "keys-sheets" in the found folder are e.g. placed in copy in several places in the folder; the folder does not contain "keys-sheets" for all the experiments, which are described in the papers selected by the Panel and which are conducted in the lab of Milena Penkowa according to the questionnaire responses; and several "key-sheets" are un-dated or with incomplete information on the animals used or the experiments conducted on these animals.

Due to the disorganised Key folder found and the shortcomings in several of the "key-sheets" the connections between the found keys and the experiments in the selected papers could be established only with some probability, not with complete certainty.

Ad B. The found slide boxes

Based on the found keys, the Secretariat found 237 slide boxes and several slide trays with primary material, which could be related with reasonable probability to samples behind the selected papers. The found primary material includes several boxes with stained sections, but also several slide boxes with un-stained slides. On some of the found boxes the label with the key is supplemented by indication of stainings done on the sections in the box. Many of the slide boxes contain a list of stainings and groups inside the lid.

Annex 3.2.3.1 contains the catalogue on the found samples and their possible relations to the selected papers.

The MP archive contains several hundred slide boxes and trays, most of the boxes with space for 200 slides, and the Panel has assumed that the slides in the archive constitutes the complete material from Milena Penkowa's lab and office.

A number of slide trays and boxes, labelled with some of the keys identified as maybe associated with the selected papers, were found in the freezers in the archive, including in the -80 freezer found shortly before the Panel's April meeting 2012. However, further investigation of the frozen slides showed that these samples were not relevant in relation to the Panel's investigations of the selected papers. Annex 3.2.3.2 reports on the Panel's study of the contents of the freezers.

Ad C. Written documentation and photos found

On the hard disc containing all files from Milena Penkowa's computers, the Secretariat found some documents which may constitute lab records/protocols for the performed immunohistochemistry (on "SUND Penkowa 2\D.\Mildocs\counts\"). However, such lab records/protocols were only found for 9 of the selected papers, namely papers A13, A63, A96, A104, A108, A124, A136, A140, A143. In several cases the Secretariat found the same lab protocol in several editions with different dates.

In addition, the Secretariat found some colour photos of stained sections which with some probability are background documentation for some of the selected papers on experiments involving humans, namely papers A8, A16, A33, A40, A211.

Furthermore, the Secretariat found hardcopies, in the MP archive, of lists with information on patients which may be associated with the papers A90 and A207.

The Secretariat did not succeed with finding any correspondence with the scientific journals on the selected papers, neither on the hard-disc nor in the rest of the archive.

The files in annex 3.2.4.1 contain the found lab records and photos, besides the found key sheets, for each selected paper. Please note that the found hardcopies that may be associated with A90 and A207 are not included in the annex files, as these lists indicate names, CPR numbers and examinations/diagnoses of patients.

Ad D. Found procedure instructions and data sheets on antibodies

The three enclosures to Milena Penkowa's questionnaire response of August 2012 describe procedures used for immunohistochemistry work such as cutting and staining of experimental tissue.

In addition, at the visit to the MP archive 20 April 2012, the Secretariat has found well organised folders with d*ata sheets* on antibodies, prepared by the respective vendors of the antibodies.

The Secretariat also found a folder containing sheets with staining instructions for students and technicians, i.e. descriptions on how to conduct specific stainings, possibly elaborated by Milena Penkowa, dated in 2009 and 2010. However, the Secretariat has not succeeded in finding folders with similar sheets in the archive for years earlier than 2009.

The folders found 20 April did not contain any protocols documenting the control experiments, necessary to determine the specificity of the immunocytochemical reactions.

The found datasheets and staining instructions are further described in annex 3.2.5.1.

Ad. E Documentation obtained directly from co-authors

The Panel has obtained the following material for some of the selected papers directly from co-authors:

- Stained slides behind papers A84 (from C. Scheede-Bergdahl and F. Dela) and A8, A40 and A211 (from B.K. Pedersen).
- A written report by co-author B.K. Pedersen informing about the completion of papers A8, A16, A33, A38, A40 and A211 attached as annex 3.2.4.2. (and 3.2.4.2.A) (This information was supplemented by micrographs and photos delivered on a USB stick and a CD, both of which have been studied by the Panel but are not attached to the report)
- Written report and photos of slides from C. Scheede-Bergdahl and F. Dela informing about the research described in paper A84 including a report on a verification test attempt by a co-author to verify some of the results after publication of the manuscript. This documentation is included in annex 3.2.4.1-found-docum-A84.
- Information by telephone from co-author P.B. Hansen on the system used for sub-classification of Hodgkin's Lymphoma in paper A90.

Ad. F Documentation for the animal experiments in three selected papers

Specifically, the Secretariat has obtained and examined documentation for the conducted animal experiments in the 3 papers A73, A208 and A302. According to the questionnaire responses for these papers, *all* the animal experiments were conducted at the Panum Institute by Milena Penkowa in collaboration with some of the co-authors on animals for which she was responsible.

However, the experiments and number of animals described in the 3 papers exceed the corresponding experiments and animals recorded in Milena Penkowa's animal journals, i.e. the official records on all Dr. Penkowa's animal experiments at Panum, approved annually by Dyreforsøgstilsynet (the Danish Animal Experiments Inspectorate).

Therefore the Secretariat has searched for and obtained documentation on similar experiments and animals recorded in animal journals of one of the co-authors (A. Larsen, Aarhus University).

The co-authors' questionnaire statements on that all the animal experiments were conducted at Panum, are assumed to be based mainly on memory. Therefore it is not unlikely that the similar animal experiments conducted at Aarhus University constitute part or full basis for the animal experiments described in the 3 papers.

Annex 3.2.8 contains a more detailed report on the Secretariat's examination of these papers and the obtained documentation.

3.2.3 Found information on overall rules/guidelines for handling of material and documentation of experiments

During the archive visits and requests to diverse sources, the Secretariat has obtained the following information on overall rules and guidelines in connection with handling of material and documentation of experiments:

National rules on animal experiments
From various websites the Secretariat has obtained information on the national rules for how to document animal experiments. These are described in annex 3.2.6.1. The national rules meet the EU rules on this issue.

SUND's rules on animal experiments and handling of experimental animals
All the experimental animals at SUND are housed in the Department of Experimental Medicine, from which the Secretariat has obtained information on SUND's procedures for housing and handling of animals. These procedures are presented in Annex 3.2.6.1 together with the national rules on animal experiments. In addition annex 3.2.6.2 contains a report elaborated by the Secretariat on practice in the previous lab of Dr. Penkowa for documenting animal experiments and lab work, based on information obtained from various persons at the Faculty.

(Lack of) overall rules/procedures for conducting and documenting immunohistochemistry experiments at SUND
At the Panel's meeting with Ulla Wewer, Dean at SUND, on 12 April 2012, Ulla Wewer informed that SUND has not had any formal rules for good scientific practice specific for the Faculty. (The minutes from the meeting are attached as annex 3.3.4). According to a memorandum of 10 April 2012 from Albert Gjedde, Head of Department for Neuroscience and Pharmacology there are also no formal rules/guidelines for procedures for how to document lab work in this department, in which Milena Penkowa worked until she left the University in 2010. (The memorandum is attached in annex 3.2.6.3).

However, there are of course some practices for documenting lab work such as immunohistochemistry experiments at the Faculty and its departments. The report in annex 3.2.6.2 describes some of the practices used in the group of Dr. Penkowa.

Furthermore, during the interview 12 April with Albert Gjedde, the Panel learnt the Professor Gjedde had established clear procedures for quality control of the work of Dr. Penkowa after his appointment to Head of Department in December 2008.

Rules for PhD projects/students at SUND
SUND's rules for PhD students (see http://healthsciences.ku.dk/phd/apply/ (in English)) appear rather similar to the rules in comparable countries. They include demands for specification of research plan, supervisor etc.

Rules and permissions for experiments (investigations) involving humans
Although Milena Penkowa has not been operative in the human health experiments presented in papers co-authored by her, the Secretariat has searched for and obtained

information on the national rules for the experiments of this kind conducted in the papers. In addition copies of the permissions for these experiments were obtained. Annex 3.2.6.4 describes the rules and shows a list of the permissions associated with the papers co-authored by Milena Penkowa on human health experiments.

3.2.4 Found documentation for the conducted animal experiments

During the archive visits and requests to diverse sources, the Secretariat has obtained the following documentation for the conducted animal experiments:

- All Milena Penkowa's permissions for animal experiments issued by the Danish Animal Experiments Inspectorate (Dyreforsøgstilsynet). Annex 3.2.7.1 shows an overview of all the permits and their contents.

- All Milena Penkowa's animal journals (i.e. log-records on Dr. Penkowa's animal experiments on Panum, approved by the Danish Animal Experiments Inspectorate, for the years 1999-2000 and 2003-2009. Annex 3.2.7.2 shows an overview of the obtained journals and their contents.

- Milena Penkowa's so-called "animal-book-diary" which appear to be a sort of draft for the official, approved animal journals for the years 1998-1999, 2004-2006 and 2009. Diaries for the missing years have not been found. Annex 3.2.7.3 shows an overview of the obtained diary and its contents, including a comparison with the official animal journals.

- The so-called project plans of Milena Penkowa. According to The Faculty of Health Sciences, any researcher must fill in and deliver a project plan together with a so-called animal requisition (see below) in order to obtain animals for experiments to be housed at Panum. Among others, a project plan must specify the planned experiments and refer to the animal permission allowing the animals to be used for these experiments. Annex 3.2.7.4 shows an overview of the obtained project plans and their contents.

- So-called animal requisitions of Milena Penkowa. The Secretariat has obtained only a minor part of these animal requisitions, i.e. requisitions only from the period 2004-2009. Annex 3.2.7.5 contains a report on the search for and obtainment of animal requisitions, including overview of the obtained requisitions and their contents.

Invoices for animal purchases 2000-2002

Among the above-mentioned found materials there is no documentation for the animal experiments and animals used by Milena Penkowa in 2001 and 2002.

However during the Panel's meeting with Milena Penkowa 12 April, she informed the Panel that she has kept folders containing copies of all receipts for her purchases and other expenses, including receipts for animals purchased. During a visit to the archive 20 April, the Secretariat thus found those folders and copied all the present receipts for animals purchased in the years 2000, 2001 and 2002, including some receipts for animals immunised, and strains maintained, at other labs than Panum (in Denmark and Spain). Annex 3.2.7.6 reports on the found animal invoices and the study of those.

The result of the study is that according to the invoices, mainly mice and only 4 rats, have been purchased by Milena Penkowa in 2000-2002.

Furthermore, all the found invoices for housing, maintenance and/or immunisations at other labs than Panum (in Spain and Denmark) are for housing, maintenance and/or immunisations of *mice*, cf. the annex.

3.2.5 Found information on Milena Penkowa's employment responsibilities and group members

Information on Milena Penkowa's job responsibilities and group members has been obtained from SUND's secretariat and the Department of Neuroscience and Pharmacology. It is described in annex 3.2.9.

3.3 The Panel's meetings with key-persons

During its meeting at Panum 11-13 April, the Panel met with the following key-persons and obtained supplementary information to the found documentation:

- Lab technicians Hanne Hadberg and Pernille Froh
- Associate professor Jørgen Kurtzhals, co-author of 4 papers with Milena Penkowa
- Professor Marianne Juhler, co-author of 1 paper with Milena Penkowa
- Dean, Professor Ulla Wewer and Head of Department of Cellular and Molecular Medicine, Professor Ole William Petersen
- Prorector Thomas Bjørnholm
- Head of Department of Neuroscience and Pharmacology, Professor Albert Gjedde (SKYPE meeting)
- Milena Penkowa.

Associate Professor Jørgen Kurtzhals and Professor Marianne Juhler were invited on request from Milena Penkowa. None of the co-authorships of Jørgen Kurtzhals or Marianne Juhler are among the papers selected by the Panel. Furthermore, the Panel had invited Lab technician Magdalena Kus, Professor Agnete Larsen and Senior researcher Meredin Stoltenberg on request from Milena Penkowa. These three persons were not able to meet the Panel 12 April, though.

From Hanne Hadberg, Pernille Froh, Jørgen Kurtzhals and Marianne Juhler the Panel achieved information on their respective collaboration with Milena Penkowa, including the procedures for documentation of experiments and handling and storing of research material. Ulla Wewer, Ole William Petersen and Albert Gjedde provided information on the procedures of SUND, respectively the departments in which Milena Penkowa has been employed, for documentation of research and handling and storing of research material.

The Panel met with Thomas Bjørnholm, as he is responsible for University of Copenhagen's initiation of the investigation. The Prorector was abroad when the Panel met for the initiation meeting in October 2011, and he therefore met with the Panel this time to briefly discuss the investigation.

From Milena Penkowa the Panel obtained supplementary information on the procedures for her handling of experimental material and her documentation of experiments. In addition the Panel received Milena Penkowa's view on the problems with finding documentation in the archive.

The minutes from the meetings with the key persons are attached in annexes 3.3.1-3.3.7.

The Panel had also invited Professor Bente Klarlund Pedersen for a meeting. Bente Klarlund Pedersen has co-authored 6 of the papers selected by the Panel. Bente Klarlund Pedersen was not able to attend the meeting, but as indicated earlier she submitted instead a detailed report on the 6 co-authored papers selected by the Panel (See annex 3.2.4.2 and 3.2.4.2.A), and some original slides and photos related to some of the papers.

4. The Panel's assessments and recommendations

4.1 Strategy of the investigation

The task of the Panel has been to investigate the entire scientific output of Dr. Milena Penkowa, published before the start of the investigation, regarding potential indications for scientific misconduct. According to the Terms of Reference (ToR), 6 publications were excluded, which were already under investigation by the Police or by the Danish Committees on Scientific Dishonesty (DCSD). Furthermore, we have excluded 23 papers which are book chapters, reviews, abstracts, conference proceedings and announcements of retractions. We have found these types of papers not relevant for further investigation, as the research addressed in them is more thoroughly presented in the primary scientific papers.

The remaining published articles (n=79) were each evaluated in detail by members of the Panel. For each paper we obtained written information on the role of the co-authors and of Dr. Penkowa regarding the history of data acquisition, the planning and completion of the studies and the preparation of manuscripts. In this way we identified manuscripts, in which Dr. Penkowa had not conducted the experiments or other research. These manuscripts were excluded from further investigation, as the task of the Panel has been to exclusively investigate the research of Dr. Penkowa.

After detailed reading of the remaining publications, the Panel selected 26 of these, in which we identified aspects that warranted more detailed investigation. These aspects included (Bibliographic data for the 26 selected papers are presented in section 3.2.1 and annex 3.2.1):

a) Inconsistencies between the described methods and the results or between the results, described in the text, and the respective photographic images,
b) unusual patterns of antigen expression, shown by immunocytochemistry,
c) questions regarding quantitative data, and
d) questions concerning documentation for animals used for the experiments.

For these papers, original slides and written documentation that with some probability could be associated with the identified papers, were found in the archival rooms, which contain the content of Dr. Penkowa's laboratory and office, and from other sources (some of Dr. Penkowa's co-authors, the Department for Experimental Medicine, which houses all animals at Panum, the Faculty of Health Sciences and more).

Regarding animal experiments, for which Dr. Penkowa had responsibility, the Panel analyzed animal experiment permissions, invoices for purchased animals and animal journals and

investigated to what extent the information found in these documents was in agreement with animal numbers and experiments, described in the publications.

The material, which was found, was analyzed in detail during the site visit of the Panel at the Panum Institute on April 11-13, 2012.

In order to obtain a better insight into the organization of Dr. Penkowa's laboratory and into the procedures of handling experiments and experimental material, interviews were performed on 12 April 2012 with Dr. Penkowa herself, the laboratory technicians Hanne Hadberg and Pernille Froh, and former collaborators (Dr. Kurtzhals and Dr. Juhler). This process was complemented by interviews with the current Dean (Ulla Wewer) and the heads of the departments in which Dr. Penkowa has been employed (Ole William Petersen, Albert Gjedde). Based on the information obtained at the interviews, the Panel obtained and examined further written documentation.

4.2 Limitations of the investigation

In this investigation the Panel was confronted with a comprehensive task, since the topic covered more than ten years of scientific activity, 102 scientific publications and an enormous amount of original material and documents, stored in the archive. For this reason the Panel had to concentrate on specific aspects and to focus on pre-selected examples of scientific papers (see section 4.1, strategy).

In addition, identification of specific material in the archive was very difficult and in some instances impossible, because the archive is unstructured and with only an incomplete index, the found folder "Key to Animals", for linking the primary samples with the experiments described in the papers. Furthermore the Secretariat was able to find only very few protocols/records on the conducted immunocytochemistry work. Even with the codes, present on the slide boxes, and the respective explanation in the „Key to Animals" folder it was only in some material possible to specifically annotate stained slides to individual animals in individual experiments. Even when this was possible, this was the case only for a subset of slides.

Since the exact annotation of sections to individual animals of individual experiments was only partly possible, we chose in addition a different strategy for evaluation. We analyzed the immunocytochemical staining patterns for individual markers in a large amount of samples from different experiments and determined, whether the quality of the staining in general was sufficient to draw the conclusions reported in the publications.

Regarding animal experiments we encountered similar problems. It turned out difficult to match animal experiments from Dr. Penkowa's laboratory with the reports documented in the Animal Journals. The major cause for this problem was that the Animal Journals from the years 2001 and 2002 were missing in the archive. Dr. Penkowa stated during the interview

that she does not know, why these Animal Journals are missing from the archive, and that they are very important, since they document a large set of relevant animal experiments. Also the interviews with the heads of department and other representatives of the University did not disclose a reason why these Animal Journals are missing. We have, however, analyzed the invoices for animals for the years 2000 to 2002.

4.3 Assessments and Observations

The Panel was impressed by the amount of material, present in the form of embedded tissue blocks and stained tissue sections in the archive of Dr. Penkowa's laboratory. Thus, an enormous amount of work and effort has been invested into scientific activities by her and her team over the decade whence she has been employed at the University of Copenhagen. This view was further supported by the interviews on 12 April 2012, in which Dr. Penkowa was described as a very hard working and highly motivated young scientist, who was also able to create a positive and productive environment for her team. The interviews further revealed that Dr. Penkowa was highly esteemed as a supportive and competent collaborator, who also was easy to motivate for new cooperative projects.

When we analyzed experiments done in collaboration, where Dr. Penkowa's role was essentially restricted to pathological analysis, we found no reason to doubt that the material, which was sent to dr. Penkowa's laboratory from outside, was properly embedded and archived and respective sections and histological or immunocytochemical stains were performed, as outlined in the respective papers. Evaluation of pathology with conventional neuropathological techniques and commonly used and established imunocytochemical markers was, in general, fine (e.g. GFAP, Lectin). Findings, reported in the papers, could be verified in many instances by analyzing the respective slides, and the photographic documentation in the papers reflected what was seen in the original slides. Furthermore, publications, which were performed in collaboration with other groups and where the actual data were gathered by students from other laboratories under Dr. Penkowa's supervision, did not raise suspicion, and this impression was also confirmed in the interviews with Drs. Kurtzhals and Juhler.

Potential problems, however, were identified, when the published papers, in which the data were predominantly generated and interpreted by Dr. Penkowa, were analyzed in detail in relation to the material found in the archive. These problems were originally detected in the analysis of the 26 specific publications, which had been selected by the Panel in the course of the strategy, outlined above, and mainly in the papers published in the years 1999 to 2005. However, problems were also detected for papers published later. In addition, during the Panel's further studies, problems were identified in some of the papers which the Panel had not selected in the first round. The findings include the following aspects:

a) Problems related to the quality control of immunohistochemistry of cytokines, growth factors and markers for oxidative damage,

b) potential problems regarding the validity of published quantitative data,

c) discrepancies between animal numbers in the publications and actually documented experiments, and

d) inconsistencies regarding photographic documentation, including discrepancies between published images and changes seen in the actual slides.

Problems related to the quality control of immunohistochemistry of cytokines, growth factors and markers for oxidative damage

In addition to basic neuropathological analysis, many of the publications contain data on expression of inflammatory markers, such as cell type specific antigens, cytokines, growth factors and molecules induced in the course of cell damage. For many of these factors (in particular cytokines and growth factors) there is a controversial literature, to what extent their specific detection by immunocytochemistry in fixed and embedded tissue is possible. Dr. Penkowa's publications contain detailed descriptions regarding expression of these factors in tissue from e.g. experimental brain lesions or muscle biopsies, including very precise quantitative data on cells, which express them. For this reason the Panel specifically focused on the analysis of sections from the archive, which could document the respective findings.

The Panel was not convinced by the staining patterns in the original slides. In many sections no or extremely weak staining was seen, which could not be explained just by fading of reaction product due to prolonged storage. In others the staining pattern suggested non-specific binding of primary or secondary antibodies. The Panel thus enquired how immunocytochemistry for such markers was established in the laboratory. Written documentation (IHC protocols, staining instructions) as well as the information from Dr. Penkowa and technicians Hanne Hadberg and Pernille Froh at the meetings on 12 April revealed that in essence the guidelines from the antibody data sheets were followed and that different dilutions of the primary antibodies, antigen retrieval methods and immunocytochemical amplification procedures were tested. However, for the selected papers, with a single exception, the Panel did not find documentation or microscopic slides describing or showing the results of technical control experiments for staining. Furthermore, there were no positive controls for the immunohistochemistry of non-routine markers (cytokines, growth factors or CD markers).

In contrast, in nearly all the publications detailed account is given regarding the immunocytochemical specificity controls, including controls with omission of primary antibodies, the use of normal rabbit, donkey and mouse serum as primary antibodies, of isotypic IgG instead of primary antibody as well as pre-absorption of primary antibodies with peptides. In the course of the meeting 12 April with Dr. Penkowa, she claimed that the respective controls have been performed, except when the same antibody is used again and

again, and that immunocytochemistry, including the control experiments, were performed by the technicians, who worked for her. It was not possible for us to find microscopic slides or written documentation for these extensive control experiments described in the publications. Furthermore, during the meeting 12 April with Hanne Hadberg and Pernille Froh, who had been instrumental in the staining (see acknowledgements in the scientific papers) for a period of several years, the two technicians told that to their memory such controls had not been performed. They further stated that they had raised the issue of controls in the interaction with Dr. Penkowa and had been told that these controls were not necessary. However, according to other collaborators, regarding papers published later than 2005, and where students from other laboratories were involved, appropriate controls were included and sections were analyzed by the research fellow together with Dr. Penkowa and the collaborator.

Problems with Quantitative Data

A substantial number of Dr. Penkowa's publications contain quantitative data on the number of cells, expressing immune associated molecules in lesions and control tissue. In most instances these quantitative data are based on counts, obtained from 3 animals per experimental group and time points. This is in general insufficient to obtain reliable data in in vivo experiments. In addition, the quantitative data show a degree of homogeneity within the respective groups, which is highly atypical for in vivo experiments. The Panel, thus, analyzed in detail the microscopic slides from which these quantitative data were obtained. As already mentioned above, the specificity of the immunocytochemical staining was questioned by members of the Panel for many markers described in the publications. An even more serious concern was that for many markers the Panel members could not clearly see in the original slides, what was counted at all. The poor quality of the immunohistochemical results as observed by the Panel in the available slides is incompatible with the precise quantification of the results or the photographs presented in the papers.

In this context it has to be noted that in the publications analyzed by the Panel all quantitative data were exclusively determined by Dr. Penkowa herself. There were apparently no systems of blinding or of independent confirmation established.

Problems with Animal Numbers

The question regarding discrepancies between animal numbers in the publications and in the actually documented experiments was not a prime focus of this investigation, since the respective publications (rat EAE experiments: paper A102 and Op mice: paper A71) have been reported before to the police and the DCSD respectively. Animal Journals from the years 2001 and 2002, which are relevant for the rat EAE experiments were not found in the archive. In the invoices for animals we did not find rat numbers, which could match the published data on experimental animals.

It is, however, relevant for this investigation that the publications A108 and A140 report findings based on the same animals as described in publication A102. In case the police investigation concludes that the experiments presented in A102 have not been performed as published, the same applies to the other two publications (A108 and A140).

Discrepancies between published figures and original slides

When analyzing the marker for T-lymphocytes (CD3) in the original slides of experiments related to autoimmune encephalomyelitis and to neurodegeneration (6-AN-induced), none of the slides showed a staining which resembled T-lymphocytes. Furthermore, the slides looked completely different from those shown in the respective figures (figure 4 of paper A13, figure 5 of paper A104, figure 2 of paper A5) and it was not possible to find out how such photographic illustrations could have been made from these slides.

Analyzing paper A84 on the expression of methallothionein very clear differences between muscles from healthy individuals under exercise compared to the muscle biopsies of the other patient groups is shown in the respective figures. This difference is hardly visible in the original slides, raising the suspicion that the micrographs have been edited to enhance any difference in staining intensity that may have been observed in the slides. These doubts are further supported by the fact that the described differences could not be confirmed by using Western blot performed by a co-author after publication of the manuscript.

4.4 Interpretation of the findings in relation to the Terms of Reference

The Terms of Reference specifically have asked to analyze Dr. Penkowa's publications regarding scientific dishonesty. Obviously it is difficult to draw the line between unintentional errors and intentional falsification. However, the Panel sees a suspicion of potentially intentional misconduct of Dr. Penkowa in the following areas:

a) Publication of animal experiments, which (at least regarding animal numbers) may have not been performed as published. This involves publications A108 and 140. These two papers are based on the same animal experiments as the paper A102 which has been reported to the Police and is not included in the Panel's investigation. The outcome of the Police investigation will thus apply to A108 and A140 also, and the Panel therefore decided to not assess these two papers any further or analyse the found slides associated with the two papers.

b) Publication of immunocytochemical control experiments, which may not have been performed as described in the publication. This involves the following papers: A3, A11, A65, A76 and A81)

c) Publication of micrographs, which may not be derived from the original material of the respective experiment (papers A5, A13 and A104), or which may have been edited to strongly enhance a difference in staining intensity, which is hardly visible in original sections (paper A84). Whether there are additional original slides, which show the documented findings cannot be definitely excluded.

d) Reporting of quantitative data, which have little or no basis on the facts seen in the original slides (papers A3, A5, A11, A13, A57, A65, A67, A81, A104, A136 and A138). It cannot be completely excluded that there are still further slides, which were not available to the Panel but represent the basis for this quantitative analysis. This is, however, unlikely, since the Panel had access to a very large number of slides from the respective experiments, clearly labeled for immunocytochemistry for the respective antigens.

Overview of the scientific papers for which the Panel has found suspicion of scientific dishonesty

Table 2 below provides an overview of the thus 15 scientific papers for which the Panel finds suspicion of potentially intentional scientific dishonesty of Dr. Penkowa, including indication of the areas about which the suspicion concerns. The Panel's specific assessments of each of these papers are indicated in the assessment forms in annex 4.1.1.

Table 2. The papers for which the Panel finds suspicion of scientific dishonesty

A.no	Title of paper and other bibliographic data	Areas [1)]
3	Altered central nervous system cytokine-growth factor expression profiles and angiogenesis in metallothionein-I+II deficient mice. Penkowa M, Carrasco J, Giralt M, Molinero A, Hernández J, Campbell IL, Hidalgo J. J Cereb Blood Flow Metab. 2000 Aug;20(8):1174-89.	b), d)
5	Altered inflammatory response and increased neurodegeneration in metallothionein I+II deficient mice during experimental autoimmune encephalomyelitis. Penkowa M, Espejo C, Martínez-Cáceres EM, Poulsen CB, Montalban X, Hidalgo J. J Neuroimmunol. 2001 Oct 1;119(2):248-60.	c1), d)
11	Astrocyte-targeted expression of IL-6 protects the CNS against a focal brain injury. Penkowa M, Giralt M, Lago N, Camats J, Carrasco J, Hernández J, Molinero A, Campbell IL, Hidalgo J. Exp Neurol. 2003 Jun;181(2):130-48.	b), d)
13	Astrocyte-targeted expression of interleukin-6 protects the central nervous system during neuroglial degeneration induced by 6-aminonicotinamide. Penkowa M, Camats J, Hadberg H, Quintana A, Rojas S, Giralt M, Molinero A, Campbell IL, Hidalgo J. J Neurosci Res. 2003 Aug 15;73(4):481-96.	c1), d)
57	Impaired inflammatory response and increased oxidative stress and	d)

	neurodegeneration after brain injury in interleukin-6-deficient mice. Penkowa M, Giralt M, Carrasco J, Hadberg H, Hidalgo J. Glia. 2000 Dec;32(3):271-85.	
65	Interferon-gamma regulates oxidative stress during experimental autoimmune encephalomyelitis. Espejo C, Penkowa M, Sáez-Torres I, Hidalgo J, García A, Montalban X, Martínez-Cáceres EM. Exp Neurol. 2002 Sep;177(1):21-31.	b), d)
67	Interleukin-6 deficiency reduces the brain inflammatory response and increases oxidative stress and neurodegeneration after kainic acid-induced seizures. Penkowa M, Molinero A, Carrasco J, Hidalgo J. Neuroscience. 2001;102(4):805-18.	d)
76	Metallothionein-1+2 deficiency increases brain pathology in transgenic mice with astrocyte-targeted expression of interleukin 6. Giralt M, Penkowa M, Hernández J, Molinero A, Carrasco J, Lago N, Camats J, Campbell IL, Hidalgo J. Neurobiol Dis. 2002 Apr;9(3):319-38.	b)
81	Metallothionein-I overexpression alters brain inflammation and stimulates brain repair in transgenic mice with astrocyte-targeted interleukin-6 expression. Penkowa M, Camats J, Giralt M, Molinero A, Hernández J, Carrasco J, Campbell IL, Hidalgo J. Glia. 2003 May;42(3):287-306.	b), d)
84	Metallothionein-mediated antioxidant defense system and its response to exercise training are impaired in human type 2 diabetes. Scheede-Bergdahl C, Penkowa M, Hidalgo J, Olsen DB, Schjerling P, Prats C, Boushel R, Dela F. Diabetes. 2005 Nov;54(11):3089-94.	c2)
104	Metallothionein prevents neurodegeneration and central nervous system cell death after treatment with gliotoxin 6-aminonicotinamide. Penkowa M, Quintana A, Carrasco J, Giralt M, Molinero A, Hidalgo J. J Neurosci Res. 2004 Jul 1;77(1):35-53.	c), d)
108	Metallothionein treatment reduces proinflammatory cytokines IL-6 and TNF-alpha and apoptotic cell death during experimental autoimmune encephalomyelitis (EAE). Penkowa M, Hidalgo J. Exp Neurol. 2001 Jul;170(1):1-14.	a)
136	Time-course expression of CNS inflammatory, neurodegenerative tissue repair markers and metallothioneins during experimental autoimmune encephalomyelitis. Espejo C, Penkowa M, Demestre M, Montalban X, Martínez-Cáceres EM. Neuroscience. 2005;132(4):1135-49.	d)
138	Treatment with anti-interferon-gamma monoclonal antibodies modifies experimental autoimmune encephalomyelitis in interferon-gamma receptor knockout mice. Espejo C, Penkowa M, Sáez-Torres I, Xaus J, Celada A, Montalban X, Martínez-Cáceres EM. Exp Neurol. 2001 Dec;172(2):460-8.	d)
140	Treatment with metallothionein prevents demyelination and axonal damage and increases oligodendrocyte precursors and tissue repair during experimental autoimmune encephalomyelitis. Penkowa M, Hidalgo J. J Neurosci Res. 2003 Jun 1;72(5):574-86.	a)

[1)] Areas in which the Panel finds suspicion of scientific dishonesty:

a) Publication of animal experiments, which (at least regarding animal numbers) may have not been performed as published.
b) Publication of immunocytochemical control experiments, which may not have been performed as described in the publication.
c) c1: Publication of micrographs, which may not be derived from the original material of the respective experiment
   c2: Publication of micrographs, which may have been edited to strongly enhance a difference in staining intensity, which is hardly visible in original sections
d) Reporting of quantitative data, which have little or no basis on the facts seen in the original slides.

Thus, the Panel has not found grounds for raising suspicion of potentially intentional scientific dishonesty of Dr. Penkowa for the remaining 64 papers. These 64 papers, and the Panel's reasons for not raising suspicion of scientific dishonesty of Dr. Penkowa, comprise the following:

- Papers for which the Panel's study of the full text of the paper revealed no grounds for suspecting scientific dishonesty in Dr. Penkowa's part of the research and results presented,

- papers for which Dr. Penkowa has played only a minor role in the research and results presented, and:

- Papers which were among the first selected 26 papers, but for which the Panel has not found basis for raising suspicion of scientific dishonesty after having examined the found documentation for these papers, due to one of the following reasons:
  - The obtained documentation has been too insufficient to validate or invalidate the research and results in the paper.
  - The obtained documentation has verified the research and results in the paper to the extent that there is not basis for raising suspicion of scientific dishonesty.

The assessment forms reporting on the Panel's findings on each of the 64 papers are included in annex 4.1.2.

4.5 The institutional framework for Dr. Penkowa's research

In terms of the institutional framework for Dr. Penkowa's research at the University of Copenhagen, the Panel commends the implementation of procedures for quality control of the work of Dr. Penkowa in the Department for Neuroscience and Pharmacology in the last 1-2 years before she left the University.

However, we find that such quality control measures should have been implemented several years earlier. In particular, we find that in her early Post Doc years Dr. Penkowa did not receive sufficient guidance and supervision, compared to international standards. The early post-doc position is one of the most critical periods in the career development of a young scientist, in this case enhanced by the fact that Dr. Penkowa submitted her Doctoral Thesis only 1,5 years after her graduation as Master, whereas a regular PhD education normally lasts at least 3 years. The reduction in time of her PhD education entails a risk of deficits in the broader research education, e.g. in good scientific practice.

We have got the impression that Dr. Penkowa worked very long hours during her PhD project, expressing her ambition to pursue a scientific career and her commitment to her scientific work. The solitary and independent position of Dr. Penkowa in her early Post Doc years, without proper coaching or quality control, together with her high level of ambition, may have contributed to the suspected flaws in her research, pointed out by the Panel in the previous sections.

Furthermore, we assess that the institutional framework in which Dr. Penkowa has conducted her research at the Faculty of Health Sciences, may have contributed to this solitary position and lack of quality control: The Faculty has not had, among others, any formal rules on good scientific practice or on mentoring of young scientists.

The Panel thus concludes that the suspected scientific dishonesty of Dr. Penkowa may have been precluded several years earlier than is the case, if the University of Copenhagen had had formal rules on good scientific practice or on mentoring of young scientists. We take the liberty to suggest some measures, which may in the future prevent such a situation:

1) Although they are not a granted remedy, formal rules of good scientific practice may help to guide young scientists in particular in their early career stages. Examples of such rules can be seen through the homepages of the Medical University of Vienna (www.meduniwien.ac.at), the Karolinska Institute (http://ki-internwebben.siteseeker.se/?q=Ethical+Council%C2%B4s+webpage&i=en, item 3, Guidelines for experimental research) or the University of Oxford (http://www.admin.ox.ac.uk/researchsupport/integrity/).

2) In addition, we find that ways should be found to grant supportive supervision to young scientists, while allowing the scientist to develop into an independent researcher.

3) Overall the system of research evaluation at the University of Copenhagen may rely too much on quantitative outcome measures than on actual quality. Counting published papers and impact factors is not a perfect criterion of scientific productivity, and judging the quality of the respective research is more important. More weight could be placed on the extent of grant funding from institutions with international peer review as an additional quality control instrument. International

evaluation of the research track at critical steps of career development would also be helpful.

List of annexes to the report

Annexes to chapter 1

1.1 Milena Penkowa's statement of 11 July 2012 with her comments to the Panel's investigation
1.2 Report on visit 7 May 2012 of The Danish Committees on Scientific Dishonesty to the archive holding the materials from Milena Penkowa's lab and office
1.3 The Panel's comments to Dr. Penkowa's statement of 11 July 2012 concerning the Panel's investigation

Annexes to chapter 2

2.1 The basis for the investigation:
2.1.1 Terms of Reference for the investigation
2.1.2 Process plan for the investigation
2.1.3 Overview of scientific papers co-authored by Milena Penkowa

(no annexes for section 2.2)

2.3 The process:
2.3.1 Letter from KU to Milena Penkowa, informing about the initiation of the investigation
2.3.2 Letter from KU to co-authors, informing about the initiation of the investigation
2.3.3 Brief description of the process of the conducted survey among the co-authors
2.3.4 Minutes from the Panel's meeting with KU 10 October 2011
2.3.5 Minutes from the Panel's panel-internal meeting 10-11 October 2011
2.3.6 Overview of the scientific papers co-authored by Milena Penkowa, split in 3 tables:
Table 1: the 79 papers which the Panel has assessed in detail
Table 2: the 6 papers which have been reported to Police or DCSD
Table 3: the 23 book chapters, reviews, abstracts, conference proceedings and retractions, which the Panel decided to not investigate.
2.3.7 The (blank) assessment form
2.3.8 Overview of types of documentation searched for, on animal experiments, procedures and more
2.3.9 Note with Milena Penkowa's remarks on the archive holding the items from her lab and office. Received by email 6 April 2012.
2.3.10 Minutes from the Panel's meeting 11-13 April 2012

Annexes to chapter 3

3.1 Result of the conducted survey:

3.1.1 Statistics on the result of the survey
3.1.2.1 The questionnaire responses, organised in an operational form
3.1.2.2 (4 files): The enclosures to the questionnaire responses, received from co-authors, incl. a file with overview of the enclosures.

3.2 The found documentation, incl. list of the papers for which further documentation has been sought:

3.2.1 List of the 26 papers selected by the Panel for further investigation (Bibliographic data)

3.2.2 Overview of the found keys and samples that with some probability are relevant for the selected papers, i.e. overviews of keys, selected papers, found samples, and overview of experiments for which keys were searched for.

3.2.3.1 Specification/catalogue on the found samples and their possible relations to the selected papers.
3.2.3.2 Report on the Panel's examination of the freezers in the MP archive.

3.2.4.1 (A folder with 23 files): Copies of the found key sheets, lab protocols and photos. One file for each of 23 of the 26 selected papers, with:

- a table indicating basic data on the paper, the wanted documentation and the found documentation
- copy of the found key-sheets, lab protocols, photos and other obtained material
  Please note that short handwritten text in "[brackets]" in the scanned key-sheets is inserted by the Secretariat.
  Concerning the further 3 selected papers, see annex 3.2.8.

3.2.4.2 Report from Bente Klarlund Pedersen on 6 of the papers selected by the Panel
3.2.4.2.A Supplementary comment from a co-author to Bente Klarlund Pedersen's report

3.2.5.1 Report on procedure instructions and data sheets on antibodies found 20 April 2012 in the MP archive
3.2.5.2 The list of contents and a few of the datasheets from the folders in the MP archive with datasheets on antibodies.
3.2.5.3 Examples of sheets with staining instructions from an unlabelled black folder in the MP archive.

3.2.6.1 Description of the Danish regulation/legislation for animal welfare in animal experiments and of rules at Department of Experimental Medicine at SUND (the Faculty of Health Sciences)

3.2.6.2 Report on practice for documenting animal experiments and lab work in Milena Penkowa's group at SUND (the Faculty of Health Sciences)

3.2.6.3 Memorandum on *Research quality control procedures at MPs department* received 8 April 2012 from Albert Gjedde, Head of Department of Neuroscience and Pharmacology

3.2.6.4 National rules on human health experiments and overview of permissions involved in the papers

3.2.7.1 Overview of Milena Penkowa's animal experiment permissions and their contents
3.2.7.2 Overview of Milena Penkowa's animal journals and their contents for the years 1999-2000 and 2003-2009
3.2.7.3 Overview of Milena Penkowa's dyrebogsdagbog ("animal-book-diary") and their contents for 1999, 2004, 2005, 2006 and 2009, including comparisons with the animal journals
3.2.7.4 Overview of the found project plans of Milena Penkowa and their contents
3.2.7.5 Overview of the found animal requisitions of Milena Penkowa and their contents
3.2.7.6 Brief report on search for documentation for animals obtained by Milena Penkowa in 2000-2002 including overview of invoices found on animal purchases and external animal housing/immunisation/maintenance of strains, 2000, 2001 and 2002.

3.2.8 Report on investigation of the documentation on the animal experiments conducted for the 3 selected papers A73, A208, A302.

3.2.9 Information on Milena Penkowa's employment responsibilities and group members.

3.3 Minutes from Panel's meetings with key-actors 12 April 2012:

3.3.1 Minutes from Panel's meeting with Lab technicians Hanne Hadberg and Pernille Froh
3.3.2 Minutes from Panel's meeting with Associate professor Jørgen Kurtzhals
3.3.3 Minutes from Panel's meeting with Professor Marianne Juhler
3.3.4 Minutes from Panel's meeting with Dean Ulla Wewer and Head of Department, Professor Ole William Petersen
3.3.5 Minutes from Panel's meeting with Prorector Thomas Bjørnholm
3.3.6 Minutes from Panel's SKYPE meeting with Head of Department, Professor Albert Gjedde
3.3.7 Minutes from Panel's meeting with Milena Penkowa.

Annexes to chapter 4

4.1 The Panel's assessments of the individual papers:

4.1.1 Assessment forms for the papers, for which the Panel has found suspicion of potentially intentional scientific dishonesty of Milena Penkowa

4.1.2 Assessment forms for the papers, for which the Panel has not found basis for raising suspicion of potentially intentional scientific dishonesty of Milena Penkowa.

List of further background materials for the investigation

(not annexed to the investigation report)

- the full texts of *all* the papers co-authored by Milena Penkowa
- The obtained animal journals
- The obtained animal journal diaries
- The obtained animal requisitions
- The obtained animal experiment permits
- The obtained project plans
- The human health ethics permits indicated in the scientific papers, obtained from the Science Ethics Committees of Region Hovedstaden
- Detailed (part) process plans for the investigation
- The total catalogue of the contents of the MP archive
- An overview about the MP hard-disc and what the Secretariat found on it, and copied.
- The Secretariat's overview of found background documentation from its first two visits to the archive (in December 2011)
- 239 boxes with primary material (slides) found in the MP archive
- Slides and USB stick and CD with information and photos from co-author Bente Klarlund Pedersen
- Slides from co-authors Celena Scheede-Bergdahl and Flemming Dela
- Lists on Hodgkin's Lymphoma and Large B cell Lymphoma patients found in the MP archive
- Notes from legal experts concerning legal aspects of the investigation
- Note from Torben Rytter, Chief legal advisor, Rector's Office, University of Copenhagen on a complaint concerning scientific practice submitted to the Dean of the Faculty of Health Sciences in 2007
- Reports to University of Copenhagen and the Danish Committees on Scientific Dishonesty (DCSD) from Henrik Galbo, respectively Bente Klarlund Pedersen (July-August 2011)
- Copies of a number of documents handed over by Milena Penkowa to the Panel at the Panel's meeting with Milena Penkowa 12 April 2012. A list of the documents is indicated in annex 3.3.7, minutes from the meeting with Dr. Penkowa.