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STATEMENT BY THE FINNISH ADVISORY BOARD ON RESEARCH INTEGRITY

Matej Orešič and Tuulia Hyötyläinen's request for a statement by the Finnish Advisory Board on Research Integrity

On 16 May 2014, the Finnish Advisory Board on Research Integrity (TENK) received a request for a statement from Matej Orešič and Tuulia Hyötyläinen. Their request concerned the procedures adopted by Technical Research Centre of Finland (VTT) in the preliminary inquiry in which they have been alleged of misconduct, and the subsequent full investigation of a specific paper (M. Orešič et al., *J Exp Med.* 2008; 205: 2975-84), in a matter related to VTT's QBIX group. M. Orešič and T. Hyötyläinen are dissatisfied with the decision given on 7 May 2014 and procedures adopted in the preliminary inquiry and the full RCR investigation.

Sequence of events according to Matej Orešič and Tuulia Hyötyläinen's request for a statement

Preliminary inquiry

The chain of events started, according to M. Orešič and T. Hyötyläinen, on 4 November 2013 when they were given a one-page statement about their temporary release from work. The written notification did not state that an RCR investigation process had been started by VTT, nor did it specify the claim of suspected scientific misconduct. M. Orešič and T. Hyötyläinen were not informed on what part of their scientific work there was the reason for suspected misconduct of research. The only written statement they received was on 12 November 2013 which was a report concerning potential collaboration between FIMM/University of Helsinki and VTT in metabolomics. The report does not specify any scientific misconduct regarding either T. Hyötyläinen or M. Orešič.

According to M. Orešič and T. Hyötyläinen, the main focus of the internal investigation was not on the suspected scientific misconduct, but on internal VTT matters, related to working methods. The preliminary inquiry found no evidence of scientific misconduct. However, VTT decided to continue the investigation.

Investigation proper: investigation of the publication Orešič et al., J Exp Med. 2008; 205: 2975-84 (“JEM paper”).

According to M. Orešič, he was informed on 22 January 2014 of the initiation of the investigation of the study *Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes*, published on 15 December 2008 in *The Journal of Experimental Medicine* (hereafter the JEM paper). M. Orešič was not given written notification of the alleged misconduct nor any information on who had made this accusation. He was also not informed on what the specific aims of the investigation were or which specific data were examined and why. Moreover, VTT did not inform him on if the investigation was a continuation of the preliminary inquiry or a new investigation. M. Orešič and T. Hyötyläinen requested VTT to provide information on the grounds for and aim of the investigation on 14 January 2014 and 27 February 2014, but they received no response. However, M. Orešič claims that VTT managers gave information about the process of the investigation to persons outside of VTT who were not involved in the investigation.

In the initial announcement of the new investigation (16 December 2013), the name of T. Hyötyläinen is noted, even though she joined VTT in 2009 and had not participated in the study leading to the JEM paper nor was she a co-author. In addition, the final report notes T. Hyötyläinen as being in the background of the investigation. VTT did not respond to the inquiries of either T. Hyötyläinen or M. Orešič about the format of the final report.

M. Orešič states that he was not interviewed by the external examiners and was not informed about the progress of the investigation. VTT sent the external evaluation reports to M. Orešič on 7 April 2014, and he was then given four days to respond, which was subsequently extended to seven days at the request of M. Orešič. This was the first time that M. Orešič was made aware that there was an actual investigation.

VTT's final report does conclude that there is no evidence of scientific misconduct. However, the report states that “there are exaggerated conclusions concerning the metabolomics part of the article”, referring to the conclusions of the external examiners. The report was sent to M. Orešič, Kai Simons and TENK. In addition, it was sent to all of the co-authors of the JEM paper as well as to the JEM journal. M. Orešič did not receive information on why the report had been submitted to these persons, nor was there any explanation as to why M. Orešič was singled out as a target of the investigation of the JEM paper among the 22 authors.

VTT's actions in the allegations of RCR misconduct of Matej Orešič

Preliminary inquiry

An international evaluation committee led by Professor Kai Simons evaluated VTT's plasma and serum metabolomics research (the QBIX group). The evaluation was done on the behalf of the Finnish Institute of Molecular Medicine (FIMM). Subsequent to the evaluation, the committee expressed its doubts on how the research data was processed in

the QBIX group. No specific cases were mentioned in the report. The first commentary on the matter was given verbally in a meeting on 1 November 2013. The written report was submitted to VTT on 11 November 2013. The international evaluation committee suspected that the scientific data was not processed in accordance with responsible conduct of research.

As a result of these accusations, President & CEO Erkki KM Leppävuori started an internal investigation. This investigation took place between 1 November and 3 December 2013. The internal auditor interviewed 20 people who had been working in the group and studied supplementary materials provided by VTT's HR department.

Based on this internal investigation, the auditor requested Professor Anne-Christine Ritschkoff and Professor Johanna Buchert to evaluate the possible scientific misconduct of research led by M. Orešič. The internal investigation found no evidence on data falsification or tampering by M. Orešič or T. Hyötyläinen. However, the internal auditor found some evidence on difficult HR relations with the QBIX group.

On the basis of the internal audit, President & CEO Leppävuori made a decision to launch an investigation proper and use an external service provider for further investigation of the matter concerning M. Orešič. All investigations regarding T. Hyötyläinen were dropped.

Investigation proper

VTT established an investigation group immediately. The investigation group concentrated on a single study by M. Orešič: *Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes*, published on 15 December 2008 in "The Journal of Experimental Medicine". The group included: Professor Anne-Christine Ritschkoff (EVP, CEO, VTT) as Chair, Professor Johanna Buchert (VP Research, Solutions for Natural Resources and Environment, VTT), secretary Laura Puronen (Internal Auditor, VTT), Dr Maria Saarela (Principal Investigator, VTT), Tuomas Kempainen (StatFinnOy, later replaced by Tale Ltd, Tommi Nurminen, Statistician) and Jouni Junnila (Oy 4Pharma Ltd, Senior Biostatistician). The investigation group began its work on 13 January. The external experts worked separately and the results were presented on 13 March 2014. Both experts had similar findings in the main issues of M. Orešič's study. The group came to the conclusion that the article contains exaggerated conclusions concerning the metabolomics part of the article.

Both reports were sent to M. Orešič and he gave his statement of defence. The investigation group sent the report to President & CEO Leppävuori on 6 May 2014. He decided that there was no evidence of data falsification or tampering found in the article. However, there were "exaggerated conclusions concerning the metabolomics part of the article".

Handling of the case by TENK

M. Orešič and T. Hyötyläinen first contacted TENK on 14 January 2014 expressing their concern that VTT did not comply with the RCR guidelines. In response to this notification,

TENK contacted VTT on 15 January, reminding the Research Centre of its commitment to following the RCR guidelines.

After receiving Matej Orešič and Tuulia Hyötyläinen's request for a statement, TENK requested a response from VTT and received one on 23 May 2014.

The Advisory Board had the following documents at its disposal:

- VTT President & CEO Leppävuori's decision to start the preliminary inquiry, 1 November 2013
- VTT's notification of Orešič and Hyötyläinen's temporary release from work, 4 November 2013
- Evaluation of the metabolomics/QBIX group at VTT, chaired by Prof. Kai Simons, no date; submitted to TENK on 9 December 2013
- VTT's report of the preliminary inquiry, 16 December 2013
- VTT's notification to proceed with the investigation, 13 January 2014
- External evaluation report – 4Pharma, 14 March 2014
- External evaluation report – Tale, 18 March 2014
- Orešič's response to external evaluation reports on the JEM paper, 14 April 2014
- VTT President & CEO Leppävuori's decision, 7 May 2014
- E-mail correspondence between Orešič, Hyötyläinen, Kari Larjava, Anne-Christine Ritchkoff and Laura Puronen, between 6 November 2013 and 9 May 2014
- Matej Orešič and Tuulia Hyötyläinen's request for a statement, 16 May 2014
- VTT's response to Orešič ja Hyötyläinen's request for a statement, 23 May 2014
- Orešič and Hyötyläinen's response to VTT's response, 20 September 2014

The Advisory Board discussed the case at its meeting on 12 June 2014. A working group of TENK actors was established to prepare a statement; the members of the working group included Director Arja Kallio, Chief Legal Counsel Ari Suomela, University Lecturer Pekka Louhiala and Secretary General (acting) Iina Kohonen. The case was processed under the 2012 RCR guidelines, a set of instructions to which VTT had agreed and committed. TENK made a decision on its statement at its meeting on 7 October 2014.

Assessment by the Finnish Advisory Board on Research Integrity

It is the task of TENK to evaluate research and science from a point of view regarding research ethics. It can submit an evaluation on whether there was a violation on responsible conduct of research or if the RCR investigation process in question was carried out properly under the TENK guidelines. TENK does not take a position on scientific debates, copyright or, for example, issues on professional ethics or employment disputes in its statements. TENK also does not take a position on events that have taken place after the start of an RCR investigation process.

Question concerning the actions of VTT on beginning a preliminary inquiry

According to M. Orešič and T. Hyötyläinen, they did not receive written notification that an RCR investigation process had been started by VTT. The only written statement they had obtained concerning this process was notification on their temporary release from work. The notification did not state that an RCR investigation process had been started, nor did it specify the claim of alleged scientific misconduct.

The purpose of the preliminary inquiry is to initially determine the validity of the allegations of scientific misconduct that are stated in the original notification and the evidence that had been put forth in support of these allegations. The allegation of a violation of responsible conduct of research must be submitted in writing to the rector or director concerned. This statement must specify what kind of violation is involved and substantiate the allegation.

If a decision is made to conduct the preliminary inquiry, the instigator of the allegation, the person alleged of misconduct and TENK must be notified immediately of the inquiry and of the grounds for it. The following parties will need to be heard during the inquiry: the person alleged of misconduct, the instigator of the allegation and, if necessary, experts and other persons involved.

According to the RCR guidelines, the preliminary inquiry is a tentative survey. The guidelines provide the party carrying out the investigation with enough discretion, in terms of its procedures, so that it can be carried out in a manner as necessitated by the nature of the case. However, TENK believes that the manner in which VTT began its investigation of M. Orešič and T. Hyötyläinen of allegations of RCR violations deviated from TENK's guidelines so considerably that it cannot be considered to be acceptable. VTT should have specified the alleged misconduct and M. Orešič and T. Hyötyläinen should have given written notification that an RCR investigation process against them had been started.

Question on the focus of the preliminary inquiry

According to M. Orešič and T. Hyötyläinen, the main focus of the internal investigation was not on alleged scientific misconduct, but on internal VTT matters related to the working methods in the research group. The preliminary reports state that the internal auditor found some evidence on difficult HR relationships with the QBIX group which affected their working methods, and which would have demanded more determined leadership by management.

The internal problems within the workplace are not included in the sphere of the responsible conduct of research. However, it is possible that problems in the workplace are reason for or can lead to RCR violations, so there may have been justification for investigating these issues.

Question on continuing the investigation after the preliminary inquiry

VTT's preliminary inquiry report states that no evidence of data falsification or tampering by M. Orešič or T. Hyötyläinen was found in the internal investigation. However, VTT

states that the President and CEO of VTT made a decision to use an external service provider for further investigation of the matter.

VTT did not comply with the RCR guidelines in this matter. The RCR guidelines state that on the basis of the preliminary inquiry, if the allegation turns out to be unfounded, the rector shall make a reasoned decision to discontinue the investigation process. Those to be notified of this decision include the person alleged of misconduct, the instigator of the allegation as well as TENK.

In TENK's opinion, VTT did not act in accordance with the RCR guidelines, as it brought the preliminary inquiry directly to be an investigation proper without informing M. Orešič. A separate decision on beginning an investigation proper should have been made by the CEO, resting on TENK's RCR guidelines. All parties to the inquiry should have been informed of the nature of the allegation and its grounds.

Question on the path of information during the investigation

According to M. Orešič and T. Hyötyläinen, they were not informed on what part of their scientific work was the reason for the suspected misconduct of research. Furthermore, they were not informed of the proceedings of the process.

The RCR guidelines state that in an investigation process, each phase of the procedure must be carefully documented and that the parties' right to information and other rights concerning the procedure are to be respected. One of the most crucial factors ensuring the fairness of the RCR investigation procedure is that all parties involved are heard; competence and expediency of the investigation process are also important factors.

Even though it is clear that RCR investigators must be allowed to carry out their work undisturbed, VTT did not act in accordance with the TENK guidelines. VTT should have responded to M. Orešič and T. Hyötyläinen's inquiries about the procedures. M. Orešič and T. Hyötyläinen should have been notified of the progression of the investigation and they should have been allowed to know what they specifically were being accused of.

Question on the composition of the committee that carried out the investigation proper

M. Orešič and T. Hyötyläinen are asking for TENK's opinion on whether VTT followed the RCR guidelines in the appointment of the investigation committee. They are specifically inquiring about a potential conflict of interest related to the JEM paper and VTT as a shareholder of Zora Biosciences Oy. To ensure the fairness and impartiality of the RCR investigation process, the investigation committee must have the necessary expertise in the academic discipline in question as well as legal or other expertise required. At least two members of the committee must be external to the organisation conducting the investigation. In this respect, VTT conducted the RCR investigation as instructed in the TENK guidelines. No evidence was given of a potential conflict of interest of the individual members of the investigation committee nor of VTT's role as a shareholder of Zora Biosciences Oy.

Question on the content of the report on the investigation proper

M. Orešič and T. Hyötyläinen question if VTT followed the RCR guidelines in the format of the final report of the investigation. According the RCR guidelines, the final report should contain an account of the events prior to establishing the investigation committee as well as evidence for the allegation.

VTT's final report on the investigation gives a detailed review of the chain of events up until the beginning of the investigation proper. At the same time, the composition of the research group and the actions of the investigation committee were reviewed. It however remains unclear how M. Orešič was heard during the investigation.

Moreover, the report should contain a well-founded assessment of the investigation committee to determine whether the suspected activity in each specific allegation in the written notification constitutes a violation against or disregard towards responsible conduct of research.

VTT's final report concludes that there is no evidence of scientific misconduct. The report also states that "there are exaggerated conclusions concerning the metabolomics part of the article", referring to the conclusions of the external examiners. According the RCR guidelines, differences of opinion that result from the interpretations and assessments of research results are a part of academic and scientific debate and do not violate responsible conduct of research. Since the final report does not specify what kind of exaggeration there is or how it came to this result, it produced the impression that the investigation was focused on clarifying scientific debates, a factor that is not within the sphere of the RCR investigation process. Also, it remains unclear why the JEM paper specifically was chosen for a more detailed inspection.

VTT sent the external evaluation reports to M. Orešič on 7 April 2014, and he was then given four days to respond, which was subsequently extended to seven days at Orešič's request. The RCR guidelines do not provide specific instructions on how much time the parties should be given for them to reply to responses. Taking into account the seriousness of the matter, one week seems like a short time and it would have been preferable for VTT to set aside a longer amount of time to process the case.

Question on the distribution of the report of the investigation proper and the inclusion of Tuulia Hyötyläinen's name in the report

M. Orešič and T. Hyötyläinen raise the question whether VTT followed the RCR guidelines in the publication of the report and the final statement. In the final report, VTT states that the reports of the external experts will not be disclosed and only the decision of VTT President and CEO Erkki KM Leppävuori will be published. The decision was sent to all parties who have financed or otherwise been involved with the DIPP study.

This is in line with the RCR guidelines. According to TENK's guidelines, if the investigation finds that the person alleged of misconduct did not violate the responsible conduct of research, the person alleged of misconduct and the instigator of the allegation

must be notified of this decision. Furthermore, an effort must be made to publish the findings of the investigation in an appropriate publication channel if the person alleged of misconduct so desires or if there are other compelling reasons. It can be considered justifiable to give notification on the decision to the funders and other parties connected to the activities of the research group.

Another question is if VTT followed the RCR guidelines with the inclusion of Tuulia Hyötyläinen's name in the final report. Even though her name was mentioned in reference to the background of the investigation, and in order to vindicate her from other suspicions, it is unclear what the initial accusations against her were. TENK thus concludes that it was not warranted to include Tuulia Hyötyläinen's name in the final report, when no specified accusations had been made against her.

Instructions from the Finnish Advisory Board on Research Integrity

The Finnish Advisory Board on Research Integrity, as set by the Ministry of Education and Culture, formed the guidelines for the responsible conduct of research and for handling alleged misconduct (the RCR guidelines) in co-operation with the Finnish research community. The objective is to promote responsible conduct of research while ensuring that alleged violations are handled with competence, fairness and expediency.

The RCR guidelines provide researchers with a model for the responsible conduct of research. The effectiveness of these guidelines is based on voluntary commitment by the research community to adhere to them and to increase awareness of the principles of research integrity. The guidelines apply to investigations on alleged violations of the responsible conduct of research.

According to the RCR guidelines, the investigation procedures for alleged violations of the responsible conduct of research involve three steps:

- Written notification
- A preliminary inquiry
- The investigation proper

The most crucial factors ensuring the fairness of the procedures to all parties are:

- The fairness and impartiality of the process
- The hearing of all the involved parties
- The competence and expediency of the process

This requires that each phase of the investigation procedures be carefully documented and that the parties' right to information and other rights concerning the procedures are respected.

Conclusion

VTT did not specify the alleged RCR violations to the researchers alleged of scientific misconduct. This would have been essential in order to protect their rights. In addition, these researchers who were targets of both the preliminary inquiry and the investigation proper were not kept informed during the investigation process as required by the TENK guidelines.

On the basis of the above TENK concludes that **VTT did not in its investigation follow the RCR Guidelines of the Finnish Advisory Board on Research Integrity (*Responsible conduct of research and procedures for handling allegations of misconduct in Finland, 2012*)** in a proper fashion.

TENK concludes that VTT should align its procedures of investigating alleged misconduct with the 2012 Guidelines of the Finnish Advisory Board on Research Integrity.

This statement is sent for information also to the President & CEO Erkki KM Leppävuori.

Jyväskylä, 7 October 2014



Krista Varantola

Chair



Iina Kohonen

Secretary General (acting)