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Statement on DECISION, THE PROCESS FOR HANDLING ALLEGED VIOLATIONS OF THE RESPONSIBLE CONDUCT OF RESEARCH (VTT ref. 126/071/2016)

I am satisfied with the decision and the external examination reports. While the reports raised specific scientific issues typical of critical scientific evaluation such as in peer review, such matters are best discussed within the scientific community using the proper channels.

I shall point out however that any allegation of scientific misconduct must include specific claims of suspected scientific misconduct as well as the concrete evidence. If these cannot be produced while allegations are made nevertheless, more likely than not this is a case of harassment – which by itself is a violation of Responsible Conduct of Research (RCR). In the specific case of the JEM paper (Orešič M et al. J Exp Med 2008; 205: 2975-84) this is particularly relevant, because the apparent allegations were made years after the paper was published. All authors have agreed to the submission of the paper, and no complaints from the authors have been made concerning the research ethics in this paper prior to or after its submission. The JEM paper has been well received by the scientific community and the key findings of the study have been confirmed or supported by multiple subsequent studies (**Appendix 1**).

The fact that the very first published allegations concerning the JEM paper, eight years after its publication, were raised in a Finnish newspaper Helsingin Sanomat based on information from anonymous sources – is a cause for suspicion. The basis for the allegation presented in Helsingin Sanomat was the 'case report' (Figure 2 in the JEM paper), which was however manipulated in the newspaper, so that the important data were removed including six out of eight metabolites as well as the average values from control subjects. Then the case was made against me personally out of 22 authors (i.e., not against the JEM paper) based on these selected data, which included an argument that control values were not included (while being removed by the newspaper itself).

The allegations published in Helsingin Sanomat are therefore so obviously fraudulent that they should be considered as serious violations of both journalistic as well as scientific ethics. The journalistic ethics in the newspaper article is currently being investigated by the Finnish Council for Mass Media (JSN). The potential violation of scientific ethics is however particularly worrying for the Finnish research community. Any researcher and any kind of research could be the target of similar kind of fraudulent complaints, given the proper circumstances. The 'anonymous source' who presented the Helsingin Sanomat with the manipulated figure is obviously a scientist, who acquired and tampered with the research data without permission and used them for malicious purpose. Since no proper channels to address scientific concerns have previously been used, it is

evident that the allegations were fabricated with intent to cause personal harm or for personal gain.

Persistent and systematic effort to interfere with another researcher's work is unacceptable and it is also a potential RCR violation. Disregard of such unethical conduct will only encourage this type of harassment and intimidation in the future and will set a precedent which risks transforming the Finnish RCR process into a useful tool for settling private disputes between the researchers. This ought to be an important consideration if the governance and the international reputation of Finnish research are of concern – whoever the false allegers or their chosen targets might be.

Sincerely,

Matej Orešič

Appendix 1

Several of the key findings from the JEM paper were *de facto* confirmed or are supported by the subsequent studies.

1. In two independent subsequent studies in Finland (DIPP study; Orešič M et al. Diabetes. 2013; 62(9): 3268-74) and Sweden (DiPIS study, with Åke Lernmark; La Torre D et al. Diabetes. 2013; 62(11): 3951-6), we validated the findings that specific phospholipids are decreased in T1D progressors in cord blood. Notably, in the Swedish study data was both blinded to us as well as the subsequent data analyses were done in Sweden (*i.e.*, we only produced the data in blinded manner, to eliminate any potential bias). The findings were further refining the initial findings from JEM paper, identifying that the decreased phospholipids are associated with early progression to T1D. The DIPP study paper also reports a predictive model for T1D, demonstrating that lipids can be used for predicting T1D.
2. In Brazilian population, recent study by a team from Brazil has found that first degree relatives of T1D patients have decreased phospholipid levels as compared to a control group (Araujo de Pina Cabral DB et al. Diabetol Metab Syndr. 2015 Jun 10; 7: 52).
3. Longitudinal lipidomics data from JEM paper was independently reanalyzed by another group (Prof. Samuel Kaski, Aalto University) for a paper where we combined the data from children (JEM paper) with that of NOD mice (experimental model of T1D) progressing to autoimmune diabetes, using a novel statistical methodology (Sysi-Aho M et al. PLoS Comput Biol. 2011; 7(10): e1002257). Not unexpectedly, also these analyses confirmed the decreased phospholipid pattern early in life in T1D progressors, and somewhat surprisingly identified the same pattern in NOD mice which later progressed to autoimmune diabetes. The findings also included increased lysoPC at early age, as well as elevated branched chain amino acids in pancreatic islets in mice progressing to autoimmune diabetes.
4. In two metabolomics studies in NOD mice by a US based team, similarity of metabolic profiles is reported between the NOD mice progressing to autoimmune diabetes and those found in the JEM paper, specifically referring to increased branched chain amino acids and decreased phospholipids (Fahrmann J et al. Am J Physiol Endocrinol Metab. 2015; 308(11): E978-89; Grapov D et al. Metabolomics. 2015; 11(2): 425-37).
5. Using a genomics approach, two back-to-back papers published in Diabetes by two separate research teams from Finland and UK/Germany, respectively, report that proinflammatory response precedes islet autoimmunity in children who later progress to T1D (Kallionpää H et al. Diabetes. 2014; 63(7): 2402-14; Ferreira RC et al. Diabetes. 2014; 63(7): 2538-50). This is consistent with our findings from the JEM paper, where the proinflammatory lipids (lysoPCs) were found increased prior to autoimmunity.
6. In collaboration with Ramnik Xavier (Broad Institute) and Mikael Knip, combined metagenomics and metabolomics approach also identified pre-autoimmune alterations in metabolome and gut microbiota in children who progressed to islet autoimmunity and T1D (DIABIMMUNE Cohort, data analyzed at Broad Institute). Notably, increased branched chain amino acids were found associated with the observed shifts in microbiota (Kostic AD et al. Cell Host Microbe. 2015; 17(2): 260-73). In collaboration with Fredrik

Bäckhed (Gothenburg), similar associations were also found in germ-free NOD mice (Greiner TU et al. PLoS One. 2014; 9(11): e110359).

7. I am aware of two other unpublished studies in NOD mice by two different international teams, where elevated branched chain amino acids and glutamate, respectively, are found elevated in the early stages preceding the onset of autoimmune diabetes.