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28-06-2022

Subject: thesis Ms Patrycja Bielawiec

Dear delegate of the Medical University of Białystok,

As kindly requested by the Medical University of Białystok, I now have evaluated the Doctoral Dissertation of Patrycja Bielawiec. In overall, the general hypothesis studied in this dissertation is very timely and relevant given that type-2 diabetes has reached epidemic proportions globally. Accordingly, novel treatment options might lead to marked reduction of numbers of patients with diabetes. The proposed target of treatment in this dissertation is the endocannabinoid system that is maladaptively upregulated in animal models of type-2 diabetes. For this purpose, rats were subjected to high fat diet that induces type-2 diabetes, and simultaneously with cannabidiol, a potent plant cannabinoid, which is expected to block the endocannabinoid system. As a readout of the effectiveness of the treatment, body characteristics were measured, as well as lipid profiles and proteins involved in regulation of insulin sensitivity and lipid metabolism. The whole doctorate research period resulted in three publications. All three publications are in well-respected journals.

The Doctoral Dissertation contains an introductory part, in which the topic and research hypothesis are introduced. This introductory part also contains an overview of the methods and a summary of the main results. This is then followed by 3 chapters containing all three publications. The first publication (article 1) is a review, providing an overview of the effects of the main plant cannabinoids on metabolism in different mammalian tissues. The last two publications investigate the potential beneficial effects of cannabidiol treatment in rats on a high fat diet. These beneficial effects were assessed at the level of proteins involved in lipid metabolism and insulin signaling (article 2), as well as on muscle lipid profiles and proteins involved in inflammatory and oxidative stress pathways (article 3). A minor limitation in these experimental studies is that the high fat diet regime induced rather modest maladaptive changes in all the above mentioned parameters, so that the window for improvement due to the cannabidiol treatment is rather small. Despite this limitation and despite that not all these (small) maladaptive changes were improved, it is clear that treatment of cannabidiol is beneficial in this rat model of type-2 diabetes.

A final remark that I wish to bring forward is the fact that this Dissertation lacks a General Discussion section in which main conclusions drawn from the experimental studies are positioned and discussed against the prevailing view in the literature. Such General Discussion would also provide the opportunity to formulate some overarching and novel ideas that would be too

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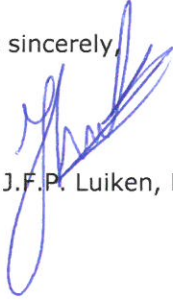
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speculative to write down into a manuscript for publication. Furthermore, in such General Discussion, the doctoral candidate could formulate her/his thoughts on future plans based on the present data and on possible implications for use of cannabidiol for treatment in the clinical setting.

In conclusion, based on the evaluation outlined above I am happy to provide a positive decision on this Doctoral Dissertation. Thus, I would recommend that the Doctoral Candidate Patrycja Bielawiec would be given the opportunity to defend her Dissertation in front of a Scientific Committee of the Medical University of Bialystok.

Yours sincerely,



Joost J.F.P. Luiken, PhD