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### **Review of the Ph.D. thesis by Yahya Sohrabi: Genetic regulation of Leishmania infection**

The thesis is devoted to the study of genetic regulation of the infection with Leishmania with the focus on interferon-induced GTPases (GBPs) and Fcγ receptor IV. Genetic control of tick-borne encephalitis virus (TBEV) infection was studied in order to look for common elements in response to L. major and TBEV. Model of recombinant congenic strains of mice was used for all these studies.

Proposed thesis is written in English, with an acceptable number of errors. Abstract is relatively long. On 4 pages it summarizes the objectives of the study, the methods used and the results obtained from each part of the thesis.

The introduction represents an extensive and well written literature review. It covers general information about Leishmania, clinical forms of leishmaniasis, immune response against Leishmania, role of GBP and Fcγ receptor IV in the infection and, finally, genetic control of leishmaniasis and Tick-borne encephalitis and mouse models used for their studies. The aims of the study are clearly formulated and have been accomplished.

The summary of the results and discussion include three chapters dedicated to the publications representing the outcome of the research. Proposed thesis are based on 6 papers, which have been published in highly impacted international journals. The discussion of each presented articles summarizes the author's results and considers them in the context of current knowledge in the field.

First part concerns the study of mechanisms influencing L. major infection. This part summarize 2 experimental studies: Sohrabi et al. Front. Immunol. 2018 (IF 5.511) and Havelkova et al (under revision) and 2 theoretical analysis: Sohrabi et al. Trend Parasitol; 2018 (IF 7.929) and Dorhoi et al. Cancer Immunol Immunother; 2018 (IF 4.846). Second part summarize results published in Kobets et al. Front Immunol; 2019, focused on mapping genes controlling parasite load after L. major infection. The aim of the third part is the study of genetic control of survival after infection with tick-borne encephalitis virus and determination its relationship to those of leishmaniasis. Results of this aim are summarized in the article Palus at al. BMC Neurosci; 2018 (IF 2. 756). Out

of 6 articles, Yahya Sohrabi is the first author of one article (Sohrabi et al. Front. Immunol. 2018), is the shared first author of one article (Palus et al. BMC Neurosci; 2018), and first and simultaneously corresponding author in Sohrabi et al. Trend Parasitol; 2018.

The weakness of this part of the thesis is that some chapters are copies of the text of the author's published articles. It means that the same information is in the thesis twice, which in my opinion, is not entirely appropriate.

Conclusion: The thesis meets requirements for Ph.D. thesis and is recommended as the basis for obtaining the degree Ph.D.

I would like to address the author the following questions:

1. Can you comment difference between mouse and human immune response to leishmaniasis? What is known about Th17 response on the outcome of the infection in humans?
2. Recently, interesting results have been published showing the difference in immune response to infections in wild-type mice compared to inbred strains. Was Leishmania infection tested on wild-type mice?
3. The author conclude that some aspects of genetic regulation of Fc $\gamma$  receptor IV in leishmaniasis are believed to be due to trans-regulation by distant genes (page 52). Do you expect that this trans-regulation will be the same in all tested strains or it is specific to the one genetic background?
4. One of the aims is to determine relationship of genetic control of leishmaniasis and tick-borne encephalitis virus. I miss discussion of this relationship at the proposed thesis. Can you comment it, explain the obtained results and what do they mean in the response to flaviviruses and Leishmania parasites?

Prague, August 31, 2019

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