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EVALUATION REPORT OF Ph.D. THESIS

Title: STUDIES ON IMMUNORECEPTOR SIGNALING MOLECULES

Author: Mgr. TEREZA ORMSBY

Ph.D. programme: IMMUNOLOGY

Charles University, Faculty of Science, Prague

I. General Comments:

The submitted thesis presents a study of complex immunoreceptor signalling events in leukocytes using several cell type models as tools to understand general mechanisms. Thesis is based on three recent publications in high quality international peer reviewed biomedical journals (International Journal of Cancer, Journal of Biological Chemistry and Blood). Tereza Ormsby is the first author of the most recent publication in the top class journal *Blood* (IF: 10,558) where important discoveries postulating role of Btk kinase in inflammation are presented. All three publications are rounded up by the general title STUDIES ON IMMUNORECEPTOR SIGNALING MOLECULES, general enough to cover NK-cell/keratinocyte interaction mediated by the ICAM-1 adhesion molecule together with characterization of the novel transmembrane adaptor protein PRR7 (potential regulator of signalling and apoptosis in activated T cells) and Btk "story". From the broad range of topics, models and methodologies mentioned in the thesis as experienced by the author is obvious, that Tereza Ormsby has obtained very general scientific education and is equipped with knowledge and skills necessary for successful immunologist. Thesis is written in English of very good quality, lacks formal mistakes and editing errors. Introductory part deals successfully on 30 pages with a hard task – to round up three quite distinct topics into one comprehensive chapter. 210 carefully selected references are properly cited thorough the text, number high enough to show author's competence and orientation in the field of the thesis. I appreciate also a crisp clarification of the author's role in the experimental design and performance in all publications. It is above any doubt that Tereza Ormsby is methodically competent (cloning, retroviral transduction, preparation of recombinant proteins, antibody characterization, immunoprecipitation, cell cultivation, stimulation of cells for signal transduction, flow cytometry) to pass the "student period" to postdoc level...

II. Specific Comments:

In the first publication (NF- κ B-dependent...) you clearly show the link between ICAM-1 expression induced by the HPV16-E6/E7 and NK cell-target cell interaction. Can you explain the link between the obvious up-regulation of the ICAM-1 by the regulatory protein derived from high risk HPV (leading to more efficient NK cell-mediated killing) and the difference between high and low risk HPVs in terms of their ability to modulate ICAM-1 expression?

PRR7 is a transmembrane adaptor protein with interesting intracellular localization. In the publication (PRR7 is a Transmembrane...) you performed co-localization studies trying to characterize the vesicular compartment positive for PRR7 with the use of endocytic markers. Do you have more recent data/speculations about the nature of the putative perinuclear PRR7 positive structure?

At p. 27 you mention that Btk is a promising target for immunotherapy and you summarize several low molecular weight inhibitors more or less specifically blocking Btk activity. Are these molecules available/did you try to use some of them (namely PCI-32765) as a tool to inhibit Btk in *in vivo* and *in vitro* experiments? Are there any human clinical trials using PCI-32765 (in dissertation you mention trials on dogs)?

III. Evaluation:

Ph.D. thesis written and submitted by Mgr. Tereza Ormsby is of outstanding quality, above the threshold required by the Ph.D. Committee in Immunology, and can be accepted as a proof of author's scientific education. I personally wish the author a successful scientific career, which has been started in prestigious laboratories under supervision of outstanding scientists.

Prague, 20th September 2011

Jan Černý

(signed)

Naformátováno: Písmo: Bookman
Old Style