



Łódź, June 23, 2023

**Evaluation of the dissertation for the degree of doctor of biological sciences  
of Adrian Kobiela, MSc, entitled:**

„The role of keratinocyte-derived small extracellular vesicles in the interaction with the  
immune system in atopic dermatitis”

performed in

The Laboratory of Experimental and Translational Immunology

The Intercollegiate Faculty of Biotechnology of the University of Gdansk and the Medical  
University of Gdansk

**under the supervision of Danuta Gutowska-Owsiak, MD, PhD, professor of the Gdańsk  
Medical University**

Atopic dermatitis (AD) is a chronic inflammatory disease, in the immunopathogenesis of which damage to the epidermal barrier and continuous inflammatory activation are observed. An important role in maintaining inflammation in the skin and exacerbating it is played by staphylococcal and fungal infections. Considering the great complexity of the immunopathology of AD, little is known about the involvement of small extracellular vesicles, the source of which are keratinocytes. Therefore, Adrian Kobiela, MSc, decided to assess the role of small extracellular vesicles secreted by keratinocytes in interaction with the immune system in atopic dermatitis.

**Assessment of the structure and substantive content of the dissertation**

The dissertation presented for the review has a typical layout and is an very carefully prepared typescript of 246 pages, supplemented with manuscripts of the published publication, as well as those under evaluation and revision, which are the basis of this dissertation. The thesis contains a list of participation in conferences, awards and scholarships, as well as attachments with statements about the co-authorship of publications.

The following papers are included into the Dissertation:

1. Kobiela A., et al. *Exposure of keratinocytes to Candida albicans in the context of atopic milieu induces changes in the surface glycosylation pattern of small extracellular vesicles to enhance their propensity to interact with inhibitory Singlec receptor. Frontiers in Immunology 13, 884530 (2022), IF=8,786 (published)*
2. Kobiela A, et al. *Filaggrin insufficiency renders keratinocyte-derived small extracellular vesicles capable of affecting CD1a-mediated T cell responses and promoting allergic inflammation. Under review in The Journal of Extracellular Vesicles (2023), IF=21.224*
3. Hovhannisyan L, Kobiela A, et al. *Excess filaggrin in keratinocytes is removed by extracellular vesicles to prevent premature death and this mechanism can be hijacked by Staphylococcus aureus an a TLR2-dependent fashion. In revision in The Journal of Extracellular Vesicles (2022), IF=21.224.*

In the *Introduction*, Adrian Kobiela, MSc, makes a broad characterization of the damage to the epidermal barrier and inflammation, which is the basis of the immunopathology of atopic dermatitis, with particular emphasis on the participation of keratinocytes and the importance of filaggrin. In the last subchapters, Adrian Kobiela, MSc, draws attention to the importance of bacterial and fungal colonization in AD exacerbations, as well as briefly characterizes small extracellular vesicles. Thus, this chapter prepares the perfect ground for understanding the numerous substantive aspects contained in the work. The assumptions and goals of the work were formulated correctly.

The results presented in the thesis suggest an important role for secretory KC sEVs in immune response in AD. *C. albicans* may promote interaction of sEVs with inhibitory Singlec receptors on APCs which may impede pathogen clearance. *S. aureus* seems to exploit the sEV-mediated removal of profillagrin and its breakdown products to avoid their antimicrobial properties. Additionally, such enhanced removal of profillagrin-related products results in further decreases of its level in epidermis, contributing to the barrier defect. KC sEVs produced on a fillagrin-insufficiency background exacerbate type 2 inflammation in the AD skin. All identified above mechanisms may intensify inflammation in AD skin by lowering barrier quality and contribution to the atopic *milieu*, and may potentially affect other tissues and organs, with relevance to the “allergic march”.

It should be emphasized that the Adrian Kobiela, MSc, used a large number of complex research methods to achieve his goals. He also obtained an outstanding amount of results. Knowledge of a wide range of methods proves the versatility and methodological skills of Adrian Kobiela, MSc, and his excellent readiness for the implementation of the research tasks. The ability to analyze and interpret the results obtained using these methods indicates the extremely dynamic scientific development of the PhD student that took place during the implementation of the research and the extensive experience that will probably pay off in the near future. The results were analyzed using properly selected statistical methods.

In the chapter *Summary of the research* summarizing the results contained in the doctoral dissertation, Adrian Kobiela, MSc concisely wrote on 10 pages of the typescript in a critical manner. The discussion is conducted in a multithreaded, yet very transparent manner, which shows the large amount of knowledge of Adrian Kobiela, MSc, and the ability to properly select arguments and literature data. It also indicates the Student's understanding of the complex issues of complicated relationships between pathogens colonizing the epidermis and the inflammatory activity of keratinocytes in the context of their release of KC sEVs.

## **Summary**

The doctoral dissertation presented for review is a reliable, valuable, original and independent scientific study of aspects concerning the role of keratinocyte-derived small extracellular vesicles in the interaction with the immune system in atopic dermatitis. Adrian Kobiela, MSc, undertook an ambitious task - he properly planned the work, substantiated the substantive basis of the conducted research, properly formulated and implemented research goals, and drew a number of interesting conclusions from the results obtained. The dissertation is a good example of a conceptual approach to a selected scientific problem. An important value of the dissertation is that it is one of the few studies on the subject chosen for research. The work makes a very large contribution to the existing knowledge in the researched field.

Therefore, I believe that the doctoral dissertation fully complies with the conditions set out in the Act at March 14, 2003 on academic degrees and academic title as well as degrees and title in the field of art (journal od laws 2003, no. 65, item 595, as amended) and in the provisions of the Act - Law on Higher Education and Science (Article 179.1 of the Act of July 3, 2018).

I hereby submit to the Committee of the Discipline Council Biological Sciences of the University of Gdańsk for scientific degrees in the discipline of biological sciences an application for admission of Adrian Kobiela, MSc, for further stages of the doctoral thesis.

Taking into account the very high value of the dissertation, the use of novel research methods and the performance of an in-depth, critical analysis of the outlined topic, as well as the unique dimension of the research obtained, I am asking the Commission to recognize Adrian Kobiela's doctoral dissertation as outstanding and accept it with distinction.

Dr hab. n med. Maciej Chałubiński, prof. UMed