



Review of the PhD thesis of Jordan Michael Holl, M.Sc.

PhD Thesis Title: “Immunomodulatory properties of novel abdominoplasty skin-derived acellular dermal matrices”

Thesis Supervisors: Dr. Andrzej Eljaszewicz and Prof. Marcin Moniuszko

THESIS EVALUATION

1. Scientific merit of the thesis

a. Originality of the research

Chronic wounds constitute a significant and growing medical problem worldwide. To date, despite extensive efforts to develop effective therapeutic strategies for the treatment of chronic wounds, limited clinical success has been achieved. With the increasing growth of populations prone to impaired wound healing (e.g., diabetic, obese and aged patients) there is an urgent need to find new therapeutic options for chronic wounds. It is known that chronic wounds are characterised by a disrupted or damaged extracellular matrix (ECM) that cannot support wound healing. Therefore, treatment strategies that are designed to replace the absent or dysfunctional ECM may be beneficial.

Significant progress has been made over the years in the development and clinical use of tissue engineered skin substitutes, among them acellular dermal matrices (ADMs). Currently, commercially available human ADMs (e.g., Alloderm, DermACELL, GraftJacket) are manufactured from cadaveric skin donors. The idea of using human skin from living patients following an abdominoplasty procedure as a source of skin for acellular dermal matrix manufacture developed previously by the team under supervision of Dr. Eljaszewicz and Prof. Moniuszko seems to be an excellent alternative.

The PhD thesis of Jordan Michael Holl is focused on characterising the immunogenic and immunomodulatory properties of novel abdominoplasty skin-derived acellular dermal matrices. These are extremely important issues evaluating the utility of abdominoplasty skin-derived ADM as a skin substitute in the treatment of chronic wounds. Therefore, I consider that the thesis contains original research and presents novel and relevant data on this topic.

b. Scientific merit of the chapters

The dissertation is written in English and consists of 11 chapters including: scientific output, introduction, materials and methods, results, conclusions, dissertation publications, summary of results, author contribution to dissertation publications, and bibliography. I consider the layout of the doctoral dissertation and order of chapters appropriate and the dissertation itself constitutes a logical and complete whole.



The core of the dissertation is based on two papers, among them one review article and one original research article that were published in high impact scientific journals and have undergone a rigorous review process prior to being accepted for publication. The author of the dissertation presented his research in Cells (IF=6.600; MNiSW=140) and Pharmaceutics (IF=6.321; MNiSW=100). The texts of the publications are clear and very well prepared. In all of these papers, Jordan Michael Holl is the first author. The authors' contributions presented in chapter 9 show that his role as an author in these publications was significant (70% and 65%, respectively). The candidate has performed all experiments, analysed data as well as written the manuscript. In my opinion these publications prove the high scientific level of the doctorate.

2. Substantial merit of the thesis

The research topic of Jordan Michael Holl's thesis is current and relevant in the context of up-to-date research in treatment of chronic wounds. The dissertation begins with the "Introduction" to the subject which directly leads to a list of several dissertation aims. Next, the author briefly describes the "Materials and Methods", "Results" and "Conclusions". In the main part of the dissertation, the two published articles were presented in their original form.

Article no. 1 consists of a literature review and includes the fundamentals of wound healing, the influence of diabetes on wound healing, and presents strategies for chronic wound treatment utilizing skin substitutes. This part contains all relevant papers for the discussed field. It is worth mentioning that most of the references are from the last decade, showing the topicality of the issue. The article is well written and provides a very good background for understanding the rest of the thesis.

Article no. 2 is the most important component of the PhD dissertation. It is an original research paper aimed at evaluating the immunogenicity and immunomodulatory properties of novel abdominoplasty skin-derived ADMs. The main and innovative result of this work is showing that the method of skin decellularisation used, influences their consequent immunogenicity and immunomodulatory properties. The authors proved that ADMs manufactured using anionic detergent SDS are characterised by low immunogenicity. However future *in vivo* studies are needed to confirm their therapeutic potential.

3. Layout and register

The layout of the thesis is appropriate. The chapters are arranged in a logical sequence and "telling a coherent story". The dissertation is well written and the English language is fluent. The quality of the graphical material is also very high.

4. Critical notes

Concerning the experimental part of the thesis I would like the candidate to answer the following minor points during defence:

1. Appropriately decellularised tissue is defined as having a *DNA* content below 50 ng/mg of the scaffold dry weight and residual *fragments* less than 200 bp in *length*. Was the residual DNA content evaluated as a content in a dry ECM weight? Were the DNA residual fragments length evaluated?
2. The *cytotoxicity* test is an indispensable part of the development of new biomaterials and *one* of the *first tests* that *must* be *performed* to verify the toxicity of materials for biomedical purposes.



Was the ADM cytotoxicity assessed? Have you observed any correlation between the immunogenicity of the differentially manufactured ADMs and their cytotoxicity?

5. Final grade

Overall, the PhD thesis by Jordan Michael Holl represents an important scientific contribution for development of new skin substitutes for treatment of chronic wounds. It should be emphasised that the results of the candidate's research have been already published in highly rated scientific journals. The published results indicate that the candidate has achieved his goals and open the way to the ultimate aim: an evaluation of the therapeutic potential of abdominoplasty skin-derived ADM *in vivo* and then introduction to clinical practice.

The thesis meets all the criteria of a doctoral dissertation and in my opinion is ready to be defended before the appropriate committee.

I hereby declare that the reviewed PhD thesis by Jordan Michael Holl meets the criteria pursuant to art. 187 of Act of 20 July 2018 The Law on Higher Education and Science (Journal of Laws of 2022, item 574) and request that the Senate of the Medical University in Białystok accepts Jordan Michael Holl for further stages of doctoral proceedings in the field of medical and health sciences, in the discipline of medical sciences.

Due to the very high quality and originality of the research and their publication in prestigious journals, I hereby request that the thesis is accepted with distinction.

September 5th, 2022

Reviewer's signature