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Report on a Thesis

Spun Fiber-based Scaffolds for Tendon Tissue Engineering

submitted

by Chiara Rinoldi, M.Sc, Eng.

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This report was prepared based on a letter sent to my attention by the Dean of the Faculty of Materials Science and Engineering – Prof. Jarosław Mizera, Ph.D, D.Sc. on 13th January 2020.

In the thesis **Chiara Rinoldi** designed, manufactured and characterised novel fiber-based scaffolds for tendon tissue engineering. To this end, electrospinning and wet-spinning techniques were used to produce particular devices, which can mimic microstructure, architecture and physicochemical, mechanical and biological properties of natural human tendons. The topic of the thesis is fully justified, because both tendon injuries and degenerative processes are very common in the society worldwide but available treatment strategies are rarely successful. Thus, in several universities and research institutes experiments aiming at development of new strategies to treat diseased tendons are undertaken.

The thesis contains seven main chapters: *I. General Introduction, II. Objective, hypothesis and scope*, four chapters in a form of typical scientific articles, describing different approaches to the design and manufacturing of artificial tendons developed by the Author and the last chapter *VII. Summary and future perspectives,* followed by *References*, *List of Figures* and *Tables* as well as achievements of the Author (*CV, list of publications and attended conferences*). The size of the thesis is rather big as compared to typical Ph.D. theses in the discipline of materials science and engineering and it accounts for 178 pages.

In *General Introduction* the Ph.D. candidate reviewed recent literature on tendons mechanical properties, injuries and treatments available. Then she focused on tendon tissue engineering and the role of mechanical, biological, chemical and architectural stimuli used to enhance tendon regeneration. Afterwards, state of the art of fiber-based engineered scaffolds was reviewed including strand, woven, knitted, braided, electrospun and wet-spun fibrous constructs. In the end, perspectives related to multi-layered scaffolds were discussed. This chapter is very well written; particularly useful and informative are two tables summarising pros and cons of all manufacturing techniques of artificial fibrous scaffolds for tendon tissue engineering. However, I have a few comments regarding both substantive content and some minor editorial errors. For example, the author used the expression "transferring forces" while writing about transferring loads by the tendons (page 17) or discussed presence of "grain tissue" during healing, while it should be rather "granulation tissue" (page 18). Moreover, the author was not coherent as regards nomenclature of the polymers, e.g. sometimes used the term "poly-L-lactic acid" (page 21) or "polylactic acid" (page 27). I would recommend in the further scientific works to use IUPAC polymer nomenclature, i.e. it should be "poly(L-lactic acid)" or "poly(lactic acid)".

In Chapter II objective, hypothesis and scope of the thesis were shown in a consistent and informative way. I do not have any negative comments except the only one on page 44: instead of "Stage 3:

Biofabrication of high aligned hydrogel yarns" it should be "Stage 3: Biofabrication of highly aligned hydrogel yarns".

In *Chapter III* the design and properties of polycaprolactone-polyamide nanocomposite scaffolds modified with silica nanoparticles for tendon tissue engineering were described. The scaffolds were prepared by electrospinning and had superior behaviour in contact with model fibroblasts as compared to the scaffolds without the nano-additive. The results were published in *Materials Chemistry B* and Chiara Rinoldi was the first and corresponding author of this paper.

In *Chapter IV* the polycaprolactone-polyamide scaffolds produced by electrospinning were coated with a GelMA-alginate hydrogel containing mesenchymal stem cells (MSC). To induce alignment and tenogenic differentiation the cells were stimulated mechanically using custom-made bioreactor. Moreover growth factor (BMP-12) was applied. The article contains a lot of valuable results suggesting that cell-material constructs produced in such a way can be used for engineering functional tendons. The results were published in *ASC Biomaterials Science & Engineering* and Chiara Rinoldi was the first and corresponding author. I have only one question: *What was the source of MSC?*, because it was not clarified in the article.

In *Chapter V* the results on wet-spinning of GelMA-alginate hydrogel bioink containing human mesenchymal stem cells derived from bone marrow (hBM-MSC) for tendon tissue engineering were presented. The cells were stimulated mechanically and by BMP-12 supplementation as already shown in *Chapter IV*. The results obtained are very promising and developed method of such constructs production is much faster than typical extrusion technology, what is particularly important if upscaling is planned. The results were published in *Advanced Healthcare Materials* and Chiara Rinoldi was the first and corresponding author. It is worth mentioning that this article was highly appreciated even prior to publication and chosen by the editors of this journal as a cover of the issue dedicated to the topic: *Building Blocks for Biofabrication Models*.

In *Chapter VI* compilation of the methods described in previous chapters was reported. In brief, two fabrication techniques, i.e. electrospinning and wet-spinning were used. Polycaprolactone-polyamide nanocomposite scaffolds modified with silica nanoparticles and enriched with BMP-12 were combined with GelMA-alginate hydrogel bioink containing hBM-MSC. The results suggest that this approach is also suitable for tendon tissue engineering.

In *Chapter VII* the author provided a brief summary of all obtained results and defined plans for the future research.

According to the letters of confirmation provided by Chiara Rinoldi and all the co-authors of the papers introduced in this thesis as *Chapters III, IV and V*, the contribution of the PhD-candidate was significant and included development of research plan, design and manufacturing of the scaffolds, evaluation of their properties, writing manuscripts and corresponding with the reviewers.

In my opinion, PhD thesis of Chiara Rinoldi is a comprehensive study of the effect of manufacturing conditions on the properties of materials in the context of their biomedical application. Such approach is the core of materials science and engineering and more specifically biomaterials engineering.

To sum up, I state that the thesis submitted by Chiara Rinoldi entitled *Spun Fiber-based Scaffolds for Tendon Tissue Engineering* fulfils all the requirements for awarding the candidate the PhD degree according to relevant law (art. 14, ust. 2, art. 20, ust. 5 Dz. U. Nr 65, poz.595 z dnia 16 kwietnia 2003 roku z późniejszymi zmianami).

Taking into account whole scientific quality of the thesis, the fact that majority of research was published in highly-ranked journals and that the PhD-candidate has exceptional scientific achievements as reflected by the high number of publications (9 papers in JCR journals) as well as oral and poster presentations at reputed conferences, my recommendation is that the PhD title is awarded to Chiara Rinoldi with distinction.

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