

Dr hab. inż. Tomasz Sawicki, prof. UWM
Katedra Żywienia Człowieka
Wydział Nauki o Żywności
Uniwersytet Warmińsko-Mazurski w Olsztynie
tomasz.sawicki@uwm.edu.pl

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DOCTORAL DISSERTATION REVIEW

The doctoral dissertation of **Ranjini Ghosh Dastidar, M.Sc.**, entitled **“A Dynamic Regulatory Model of *In Vivo* Vitamin D Responsiveness: From Transcriptomic Discovery to Systems Identification in Human Immune Cells,”** was prepared under the supervision of **Professor Carsten Carlberg** within the Interdisciplinary Doctoral School of Agricultural Sciences.

Formal basis: Resolution of the Scientific Council of the InLife Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences of June 11, 2026, appointing me as a reviewer in the proceedings for the conferment of the degree of Doctor of Agricultural Sciences in the discipline of Food Technology and Nutrition.

Legal basis: Articles 190 (2–4) of the Act of July 20, 2018 – Law on Higher Education and Science (consolidated text: Journal of Laws of 2024, item 1571, as amended).

Selection and Significance of the Topic

Despite extensive research and the widespread use of vitamin D supplements, large-scale intervention trials have often failed to demonstrate unequivocal population-level health benefits. One possible explanation for these inconsistent findings is the considerable interindividual variability in biological responses to vitamin D supplementation.

The doctoral dissertation of Ranjini Ghosh Dastidar, M.Sc., addresses this scientifically relevant problem by investigating the transcriptomic and regulatory basis of individual vitamin D responsiveness. The Candidate examines the vitamin D response index, its reproducibility and occurrence in different populations, and the molecular mechanisms differentiating individuals with high, intermediate, and low responsiveness. This research progressed from identifying *in vivo* vitamin D target genes to developing a

dynamic model of the transcription factor network underlying these differences. The selected topic is important because it extends the assessment of vitamin D responsiveness beyond the conventional measurement of serum 25-hydroxyvitamin D concentrations. Instead, the Candidate applies a functional approach based on changes in gene expression in peripheral blood mononuclear cells. The use of genome-wide RNA sequencing, longitudinal transcriptomic data, and mathematical modelling provides an opportunity to describe interindividual variability and explain its potential molecular basis.

These findings may have practical relevance for the development of personalized vitamin D supplementation strategies and for improving the design of future nutritional intervention trials. Although the dissertation has a strong molecular and computational focus, its subject is directly related to molecular nutrition, nutrigenomics, nutritional supplementation, and personalized nutrition, which aligns perfectly with the latest global research trends concerning the maintenance of homeostasis in the human body.

In my opinion, the selected topic is original, timely and scientifically significant. This dissertation addresses a clearly defined gap in the current knowledge concerning individual responses to vitamin D3 supplementation; therefore, the selection of the topic is fully justified.

Formal Evaluation of the Dissertation

The doctoral dissertation submitted for review was written in English and comprised 201 pages. It has a mixed (hybrid) form, combining a thematically coherent series of three published original research articles with one unpublished manuscript that is currently under review. The published and unpublished components are clearly identified in this dissertation.

Published original research articles

P1. Ghosh Dastidar, R., Jaroslawska, J., Malinen, M., Tuomainen, T.-P., Virtanen, J.K., Bendik, I., & Carlberg, C. (2024). In vivo vitamin D targets reveal the upregulation of focal adhesion-related genes in primary immune cells of healthy individuals. *Scientific Reports*, 14, 17552. <https://doi.org/10.1038/s41598-024-68741-9>

P2. AlGhamdi, S.A., Ghosh Dastidar, R., Rybiński, M., Alsufiani, H.M., Khoja, S.O., Enaibsi, N.N., Saif, S.F., & Carlberg, C. (2024). Evaluation of the vitamin D response index in a Saudi cohort. *Saudi Pharmaceutical Journal*, 32, 102137. <https://doi.org/10.1016/j.jsps.2024.102137>

P3. Gospodarska, E., Ghosh Dastidar, R., Jaroslawska, J., Rybiński, M., Raczyk, M., Tokarczyk-Malesa, K., Romaszko, J., & Carlberg, C. (2025). Transcriptomic profiling of immune modulation induced by vitamin D3 in the VitDPAS and VitDHiD cohort studies. *Scientific Reports*, 15, 17334. <https://doi.org/10.1038/s41598-025-02495-w>

Unpublished manuscript

P4. Ghosh Dastidar, R., Gospodarska, E., Tokarczyk-Malesa, K., Romaszko, J., Domínguez-Hüttinger, E., & Carlberg, C. (2026). Dynamic system identification defines a minimal transcription factor control architecture of human endocrine gene regulation.

The dissertation begins with abstracts in English and Polish, a list of abbreviations, and a reader's guide to the chapters. Chapter 1 presents the theoretical background, and Chapter 2 defines the objectives and research hypotheses. Chapters 3-6 summarize the four studies forming the scientific basis of the dissertation. Integrated observations are presented in Chapter 7, followed by the General Discussion in Chapter 8, Conclusions in Chapter 9, and Implications and Recommendations in Chapter 10. The subsequent chapters contain lists of figures and tables, information on publicly available datasets, references comprising 61 items, acknowledgements, statements concerning the Candidate's contribution, and formal documents. The full texts of the three publications and the unpublished manuscript are included in Chapter 18 of this thesis.

The Candidate is the first-listed author of two works, P1 and P4, and a co-first author, with an explicitly declared equal contribution to P2 and P3. Thus, she held a leading authorship position in all four studies forming the scientific basis of the dissertation. Her declared scientific contributions were primarily computational and bioinformatics and included RNA-seq data processing, differential gene expression analysis, pathway enrichment, development of response-scoring algorithms, clustering, cross-cohort comparisons, construction and reduction of transcription factor networks, mathematical modelling, data visualization, and manuscript preparation. The scope of

these contributions is described in detail in the relevant statements included in this dissertation.

The structure of the dissertation is logical and allows the reader to follow the progression from transcriptomic discovery and validation in different populations to the development of a dynamic regulatory model of transcriptional regulation underlying interindividual vitamin D responsiveness. Each chapter is clearly linked to the overall objective and research hypotheses. The tables and figures support the presentation and interpretation of the results, and information on publicly available datasets increases the transparency and reproducibility of the research.

Nevertheless, several minor formal inconsistencies should be corrected. In the declaration of authorship, the candidate's contribution is stated to be described in Chapter 15, whereas it is presented in Chapter 16. Moreover, the status of the manuscript included in Chapter 6 is described inconsistently as "submitted," "under review," and "under revision." This terminology should be standardized throughout the dissertation. These minor editorial issues do not affect the scientific value or overall assessment of this work.

In formal terms, the dissertation is comprehensive, appropriately structured, and prepared in accordance with the requirements applicable to a mixed (hybrid) doctoral dissertation. Therefore, I evaluated its formal aspects positively.

Originality and appropriateness of research tools and methods

Analytical, bioinformatic, statistical, and mathematical modelling methods were appropriately selected, aligned with the objectives and hypotheses of the dissertation, and based on validated tools consistent with current research standards. A particular strength of the dissertation is the use of a range of complementary statistical methods, which enabled the Candidate to examine multiple parameters and relationships and supported a comprehensive interpretation of the results. Overall, the methodological approach enabled the research objectives to be achieved and provided substantial evidence to support the formulated hypotheses.

I rate the originality and suitability of the research tools and methods very highly.

Substantive Evaluation and Scientific Value of the Dissertation

This dissertation addresses an important problem in molecular nutrition: interindividual variability in the molecular response to vitamin D3 supplementation. Individuals with similar increases in serum 25-hydroxyvitamin D levels may differ considerably in their transcriptional responses. Identifying the determinants of high, intermediate, and low responsiveness is therefore important from both scientific and potential application perspectives.

In the general introduction, the Candidate presents current knowledge concerning vitamin D metabolism, receptor-mediated gene regulation, and its physiological and immunological functions. She also discusses the inconsistent results of supplementation trials, the concept of the vitamin D response index, rationale for using peripheral blood mononuclear cells, and advantages and limitations of bolus supplementation. This section provides an appropriate theoretical basis for the experimental study.

The central objective of this study was to identify the molecular and regulatory mechanisms underlying individual responses to vitamin D3. Five logically connected hypotheses concern the transcriptional response to supplementation, reproducibility of the response index, presence of low responders in different populations, conserved core of responsive genes, and possibility of explaining this variability using a dynamic regulatory model.

In the first study (P1), RNA-seq analysis of peripheral blood mononuclear cells from Finnish participants identified 452 candidate in vivo vitamin D-responsive genes, with enrichment of pathways related to focal adhesion and cytoskeletal organization. The Candidate also developed an RNA-seq-based response index and classified the 25 participants into 9 high, 12 intermediate, and 4 low responders. A comparison of four consistently classified high responders with four consistently classified low responders revealed a higher baseline HLA-C expression in the former group. However, Chapter 3 of the dissertation reports 4 high, 12 intermediate, and 9 low responders, which is inconsistent with P1. Moreover, the dissertation states that 40 participants were enrolled and 25 were selected for the transcriptomic analysis. Therefore, I would like to ask the candidate to clarify these discrepancies and indicate whether the HLA-C finding should be considered a potential biomarker or a preliminary observation requiring validation in a

larger cohort. Moreover, the response index developed in P1 was based on the molecular response to a single high-dose bolus of vitamin D3, whereas conventional nutritional recommendations generally involve daily supplementation of vitamin D3. Can this response index be extrapolated to daily supplementation?

The second study (P2) evaluated the response index in a Saudi Arabian cohort using cytokine measurements in 100 participants and qPCR analysis of seven genes in a subgroup of 37 participants. However, P2 reported concordant classification for 30 of the 37 participants (81%), whereas the dissertation reported a concordance of 88.6%. Therefore, I would like to ask the candidate to clarify how the concordance reported in the dissertation was calculated and to explain the source of this numerical discrepancy.

In the third study (P3), transcriptomic analysis of 45 Polish participants confirmed their classification into three response groups. Comparison with the Finnish cohort identified 232 shared genes, and after applying more stringent statistical criteria, a conserved core of 26 genes associated mainly with TNF and NFκB signalling. The cross-cohort comparison strengthens the reliability of these findings. The identified 26-gene core was further supported by repeated supplementation data and chromatin accessibility analyses. In view of this evidence, I would like to ask the candidate what additional studies would be most important to confirm the functional significance of this gene set in vitamin D-mediated immune regulation.

The fourth study (P4) used 287 RNA-seq libraries collected from 41 participants over three supplementation cycles. The Candidate reduced a gene-regulatory network to a kernel of 11 transcription factors and 117 interactions and used ordinary differential equations to describe its dynamics. The TP53–AP1–MYC axis was identified as a potential determinant of high and low responses. This innovative approach moves beyond descriptive transcriptomics towards a mechanistic explanation of individual variability. The complexity of the proposed model raises a more general question: How reliable is the model in explaining and predicting individual responses to vitamin D3, and what further validation is required before it can be applied in nutritional or clinical practice?

Summary of the principal scientific achievements

In my opinion as a reviewer, the principal original achievements of the dissertation include the transcriptome-wide identification of in vivo vitamin D-responsive genes, the

development and cross-population evaluation of the vitamin D response index, the identification of a conserved 26-gene core, and the construction of a dynamic regulatory model indicating the potential role of the TP53–AP1–MYC axis in interindividual vitamin D responsiveness.

The theoretical background, appropriate selection and critical use of scientific literature, formulation of the research hypotheses, and interpretation of the results demonstrate that the candidate possesses extensive general theoretical knowledge relevant to the discipline of food technology and nutrition. I would like to emphasize that the doctoral candidate has achieved the principal objective of the dissertation and provided substantial evidence supporting the formulated research hypotheses. I rate her ability to critically analyze data very highly.

Her leading contributions to bioinformatic analyses, development of the response index, cross-cohort comparisons, regulatory network construction, and mathematical modelling confirm her ability to conduct independent scientific research. Furthermore, the integration of transcriptomic analyses from different cohorts with dynamic regulatory modelling constitutes an original approach to explaining interindividual variability in vitamin D responsiveness and represents a novel solution to the scientific problem addressed in this dissertation. This is an original and valuable study comprising a series of articles published in renowned international journals. The research problem addressed is of great significance in terms of advancing knowledge and practical application. This field of study calls for further in-depth research employing state-of-the-art tools, highlighting the Author's significant scientific potential and her ability to identify, formulate, and resolve a research problem of considerable social importance.

In summary, I consider the doctoral dissertation submitted for review to be of a very high substantive standard, featuring innovative elements and significant practical value.

The questions raised in this review are intended to clarify selected methodological aspects and discrepancies between the dissertation and appended publications. They do not affect my positive assessment of the candidate's theoretical knowledge, her ability to conduct independent scientific research, or the originality and scientific value of the dissertation.

Final Conclusion

I evaluate the doctoral dissertation of Ranjini Ghosh Dastidar, M.Sc., entitled “A Dynamic Regulatory Model Of *In Vivo* Vitamin D Responsiveness: From Transcriptomic Discovery To Systems Identification In Human Immune Cells”, positively. This dissertation represents an original and scientifically valuable contribution to molecular nutrition, nutrigenomics, and systems-level research on vitamin D responsiveness. The present study provides new knowledge concerning interindividual differences in the molecular response to vitamin D3 and establish a basis for the further development of personalized supplementation strategies.

In conclusion, the dissertation demonstrates the Candidate’s general theoretical knowledge in the discipline of food technology and nutrition, confirms her ability to conduct independent scientific research, and constitutes an original solution to a significant scientific problem. Therefore, this dissertation fulfils the requirements specified in Article 187 of the Polish Act of July 20, 2018 – Law on Higher Education and Science (consolidated text: Journal of Laws of 2024, item 1571, as amended).

Therefore, I request that Ranjini Ghosh Dastidar, M.Sc., be admitted by the Scientific Council of the InLife Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences to the public defense and subsequent stages of the proceedings for the conferment of the degree of Doctor in the field of agricultural sciences in the discipline of food technology and nutrition.



Signed by /
Podpisano przez:

Tomasz Sawicki

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