

**Intercollegiate Faculty of Biotechnology UG and MUG  
University of Gdansk**

Subject : Review of Mr Marcos Yébenes Mayordomo doctoral dissertation named “Integration as a solution: A multi-omic approach to cancer diseases” (2022)

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This document is a review of the doctoral dissertation of Mr Marcos Yébenes Mayordomo describing his research work carried out at the International Center for Cancer Vaccine Science under the supervision of Prof. Theodore R. Hupp and the co-supervision of Dr. Javier A. Alfaro.

During his thesis, Mr Mayordomo implemented bioinformatics approaches for the analysis of multi-omics data generated from biological samples of human biopsies coming from three different studies. The first study consisted of the integrated analysis of proteomic, genomic and transcriptomic data generated from a cohort of 400 tissue biopsies from patients with esophageal adenocarcinoma. In particular, this study identified tumor-specific genes using a methodological approach based on the characterisation of aberrant changes in gene expression between transcripts and protein levels. The second study is an analysis integrating proteomic and genomic data produced from a cohort of 20 tissue biopsies from patients with undifferentiated pleomorphic sarcoma. It revealed in particular the heterogeneity of the mutational landscape associated with this family of cancers and identified avenues for the development of personalized therapies. The last study consists of a case report to better understand the molecular alterations associated with Gorham-Stout disease through the bioinformatics analysis of the genomic and transcriptomic profiling of the diseased tissue of a patient. This latest work was published in 2022 in the journal BMC Medical Genomics with Mr Mayordomo as first author. The detailed assessment of the doctoral dissertation will take place in three steps:

- 1) Assessment, together with a justification, of whether the doctoral dissertation presents the general theoretical knowledge of the applicant for the award of the degree of doctor in a given discipline or disciplines

The general introduction of the doctoral dissertation begins with a synthetic presentation of cancer biology with a focus on cancer hallmarks which are acquired functional capabilities allowing cancer cells to survive, proliferate, and disseminate. This is followed by a synthetic description of the contributions of genomics, transcriptomics and proteomics to cancer research. For each technology, the molecular characteristics that can be extracted are described, their relevance in oncology as well as the major consortia research projects that have enabled significant progress thanks to these technologies. This introductory chapter ends with a section describing multi-omics data integration strategies applied to point mutation detection, fusion gene identification, association analysis between cis-regulatory mutations and gene expression, and the study of expression changes between transcriptome and proteome levels.

Furthermore, each of the three studies presented in the doctoral dissertation begins with a short introduction of the pathology treated and detailed descriptions of the experimental approaches to the production of omics data and the bioinformatics methods used to analyze these data.

These elements of writing show that Mr Mayordomo acquired during his thesis a good knowledge of the biology of the pathologies on which he worked, experimental technologies of data production and bioinformatics methods adapted to the analysis and modelisation of genomic, transcriptomic and proteomic data.

2) Assessment and justification of whether the doctoral thesis demonstrates the ability of the applicant to carry out scientific or artistic work independently

The research work presented by Mr Mayordomo in his doctoral dissertation starts with the definition of the biological question, then goes through the experimental preparation of the biological samples, their profiling by omics technologies, the bioinformatics analysis and integration of the produced data and ends with the interpretation of the results related to the bibliographical knowledge already published. Although Mr. Mayordomo's main expertise is bioinformatics and multi-omics data modeling, his doctoral dissertation illustrates his ability to collaborate with other experts to carry out a full scientific research project.

3) Assessment and justification of whether the doctoral dissertation provides an original solution to a scientific problem, an original solution to an application of the results of own scientific research in the economic or social sphere, or an original artistic achievement

Cancer research based on multi-omics data is an emerging field for which few standards and best practices exist for integrated data analysis. Mr Mayordomo has, with his research work, implemented bioinformatics approaches for the analysis and integration of multi-omics data allowing to move forward the molecular characterization of cancers and to contribute to the identification of new biomarkers and potential therapeutic targets.

For the study of the cohort of patients with esophageal adenocarcinoma, the original approach implemented to identify genes presenting aberrant expression changes between the transcriptome and the proteome revealed potential new oncogenes. As for the study on pleomorphic sarcoma, the combination of information from the genome, transcriptome and proteome has made it possible to refine the mutational landscape of this family of cancers and to reveal potential new targets for therapies. Finally, the first integrated analysis of genomic and transcriptomic profiling of a patient affected by Gorham-Stout disease has allowed, by characterizing the mutational landscape, to advance understanding of the genetic alterations causing this pathology.

To conclude, the bioinformatics approaches presented in this doctoral dissertation show the high potential associated with the integration of multi-omics data, when applied to oncology, and pave the way to establishing good practices for this new field of research.

Best regards,  
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