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Re: Marcos Yebenes Mayordomo dissertation

Scientific Council members:

It is my great pleasure to write this letter of support for Marcos Yebenes Mayordomo's dissertation titled, "Integration as a solution: A multi-omic approach to cancer diseases". I am an Associate Professor in the Department of Surgery at UT Southwestern Medical Center (UTSW) and have spent much of my scientific career studying lymphatic malformations (LMs) and Gorham-Stout disease. I am very active in the graduate school at UTSW and have trained 1 graduate student and served on 7 dissertation committees. I am also on the steering committee for the Genes, Development, and Disease graduate program at UTSW and am co-director of the Center for Organogenesis and Trauma Research in the Department of Surgery at UTSW. In addition to being faculty at UTSW, I am the Director of Research for the Lymphatic Malformation Institute (LMI). The LMI is a non-profit organization that funds research on LMs and Gorham-Stout disease. I provide scientific leadership to the LMI, identify new avenues of research, and facilitate the formation of collaborations among investigators studying LMs and Gorham-Stout disease. Based on my experience, I believe that I am qualified to review Marcos Yebenes Mayordomo's dissertation.

Over the past several years, significant progress has been made in the ability to generate genomic, transcriptomic, and proteomic data. The main focus of this dissertation is on the integration of multi-omic data to gain insight into the mechanisms of esophageal adenocarcinoma (EAC; Chapter 1), undifferentiated pleiomorphic sarcoma (UPS; Chapter 2), and Gorham-Stout disease (GSD; Chapter 3).

EAC is the 6th leading cause of tumor-caused death in western countries. Genomic sequencing studies have facilitated the identification of driver mutations for EAC. However, much remains unknown about the molecular mechanisms driving EAC tumorigenesis. The present study utilized DNA-sequencing and RNA-sequencing data from over 300 EAC samples and mass spectrometry proteomics from a small subset of patients to provide a complete proteogenomic characterization of EAC. This points to potential biomarkers and pathways for therapeutic targets for EAC. The work also revealed discordance between RNA and protein levels for several genes and highlighted the advantage of multi-omic over single-omic analysis.

UPS is the most common sarcoma subtype in adults and is defined as a tumor of mesenchymal origin with no identifiable line of differentiation. The molecular landscape of UPS has not been fully characterized. Here, exome sequencing (20 UPS and normal controls), RNA-Sequencing, and mass spectrometry were used to investigate the oncogenic landscape of UPS. The findings

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from this project suggest that UPSs are heterogeneously mutated and the majority of mutated genes are patient specific.

Gorham-Stout disease is a sporadically occurring disease characterized by lymphatic invasion of bone and massive osteolysis. Somatic activating mutations in *KRAS* have been identified in some, but not all, patients. Therefore, Gorham-Stout disease is likely a genetically heterogenous disease. The present study used whole-genome sequencing (WGS) and RNA-sequencing to investigate the molecular mechanisms driving the disease in 1 patient. WGS did not reveal a clear driver mutation responsible for the patient's disease. However, the RNA-sequencing data were very informative and demonstrated that VEGF-C and VEGF-D were elevated in affected tissue from the patient. It also suggested infiltration by M2 macrophages, a finding confirmed by immunohistochemistry.

Taken together, the findings described in this dissertation represent some of the first steps towards identifying new biomarkers and therapies for EAC, UPS, and Gorham-Stout disease. The experiments described in the dissertation were technically innovative and conducted with a high degree of scientific rigor. The document was extremely well written and I do not request any changes to the dissertation. In conclusion, I strongly support the acceptance of Marcos Yebenes Mayordomo's dissertation.

Sincerely,

Michael Dellinger

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