# Introduction to Resubmission

I appreciate the reviewers’ insightful feedback regarding my F30, which I believe has improved the quality of this resubmission. Below I provide a high-level summary of key comments from the reviewers and how I have addressed them in this resubmission.

One reviewer expressed concern that I have yet to publish a first-author paper. In the revised submission, I provide additional evidence for my productivity throughout my PhD training. I have earned co-authorsip on several publications, including one in *eLife* and another in currently in review. Beyond co-authorship, I am preparing two first-author manuscript using the techniques I present in this proposal. I am co-first author on a manuscript highlighting the use of wide-field micro-CT for the investigation of *Octopus*, which will be submitted to *Current Biology* by the end of August. I am first author on another manuscript focused on the phase-contrast imaging data included in aim 1 of this proposal, which will be submitted to *Modern Pathology* by the end of September.

Two reviewers expressed concern that the roles of the co-sponsors were not clearly defined. In the revised submission, I have clarified the roles of the co-sponsors. Dr. Silverman is the primary sponsor of this project and will oversee the majority of the proposed work. Dr. Cheng will co-sponsor with a focus on micro-CT and histopathology. Preliminary results to date have centered around micro-CT imaging, which has been supervised by Dr. Cheng. However, we have made significant progress towards completion of aim 1 and we provide additional preliminary data indicating its promise in the updated proposal. Dr. Silverman has been chosen as the primary sponsor of this project, as the majority of the proposed research training plan aligns with his expertise in statistical methods and machine learning. He will oversee aims 2 and 3, as well as the most critical aspects of the training plan, including coursework and self-study of topological data analysis (TDA).

One reviewer observed that the proposed work represents a departure from my training background. In the revised submission, I provide greater detail regarding my background and research training to date, indicating how my past, current, and future experience align with the proposed work. I now highlight how my undergraduate training focused on computational methods within biochemistry. I detail how my PhD coursework and training in the Silverman lab have included in-depth study of statistical methods, applied machine learning, and linear algebra, supporting aims 2 and 3. I elaborate how ongoing self-study guided by Dr. Silverman has bolstered my knowledge of TDA, preparing me for aim 2. I close with a formal plan for coursework and additional self study to cover TDA, functional data analysis (FDA), and to prepare me for an independent career in applied computational biology. I emphasize the elements of Dr. Silverman’s background that equip him to mentor me throughout this process. I emphasize Dr. Silverman’s credentials that make him the ideal mentor for my career goals and this project. Rigorous training to bolster my expertise in machine learning and statistics will include taking Data Mining (IST557) and a formal course in TDA through the math department. Please see the updated Applicant Goals and Background for Research section for additional details.

One reviewer expressed concern that the aims exhibit interdependence. In the revised submission, I include additional preliminary data in support of aim 1 to indicate its feasibility. I also bolster the alternative approaches within aims 2 and 3, highlighting the versatility of topological data analysis and its value as the field of 3D histopathology expands. Please see the updated Aims and Research Strategy sections for updated alternative hypotheses.

One reviewer pointed out that this training grant appears more suited for a career in clinical pathology than hematology/oncology. In the revised submission, I reiterate that my long-term goal is to lead an independent research program in oncology as a physician scientist. The proposed work details novel methods and study of morphological characterization in cancer. This resubmission attacks core questions in cancer biology that while applicable to clinical pathology are central to clinical oncology. These include the quantitative assessment of phenotypic heterogeneity in prostate cancer, a challenge originally identified through clinical practice which also has broad implications for the treatment of other tumors. Beyond the research elements of this proposal, I highlight that the training plan is also well-tailored to a career as an oncologist.

One reviewer requested additional biosketches from the referees for this proposal. In the updated application, updated biosketches for Dr. Warrick, Dr. La Riviere, and Dr. Tolbert are included. We are very thankful for their contributions and ongoing support for this project.

Thank you for your valuable feedback and consideration of my revised application.

Sincerely, Andrew Sugarman