**Introduction to the resubmission**

We are grateful for the insightful, detailed reviews of our original application. The reviewers enthusiastically highlighted the most innovative aspects of our proposal – particularly our outdoor “rewilding” experiments, which probe how natural environmental experience alters immune responses of inbred mice – and suggested that we should develop those elements more thoroughly. They also applauded the close integration of theory and experiment in our workflow but wisely noted that consistently mechanistic models would better elucidate immunological process. Furthermore, the reviewers offered excellent suggestions to clarify the significance of the work, especially the rigor of our hypothesis tests and generalizability of our findings. Our substantially revised application therefore improves our proposal in three major ways:

**I. Titrating environmental realism more fully into our model system.** All reviewers liked Aim 3 and expressed some disappointment that we gave it, and environmental realism more generally, short shrift. We are delighted that the reviewers share our enthusiasm for naturalizing mouse models, and we relished the opportunity to develop that aspect of the proposal. We have therefore revised throughout, to titrate in multiple environmental factors likely to alter responses to gastrointestinal nematodes, and to describe our plans under Aim 3 in more detail. Specifically, we have: A) made chronicity-promoting microbial exposures consistent across experiments by naturalizing gut microbes of all mice; we emphasize that such antigenic experience is expected to make mice better models for human immune function; B) introduced “trickle infections” to mimic realistic exposure rates and serve as an additional experimental probe of immune feedback loops under Aim 2; and C) clarified that outdoor experiments each spring/summer under Aim 3 further naturalize the system and will test rewilding-induced immune feedback loops built into our mathematical models of infection duration. Aim 3 remains highest-risk, highest-reward, but it’s better laid out AND conceptually connected to Aims 1 & 2.

**II. Deploying mechanistically explicit mathematical models right from the start to facilitate investigation of the immunological processes that determine infection duration**. We agree with the reviewers that our initial focus on a phenomenological model obscured our intention to discover the immunological processes that explain duration of infection. We previously launched into a more mechanistic model only under Aim 2. In the revised application, we introduce a mechanistic model in Aim 1, which allows us to connect our empirical hypotheses for each subsequent Aim to immunological mechanisms represented in the model. We especially focus on details of transcriptional and cytokine-mediated cross-regulation between chronicity-promoting T-helper 1 and clearance-promoting T-helper-2 responses. We also clarify that we seek to explain duration in terms of the underlying processes of immune responses and growth of parasite biomass, using mechanistic models that generate testable hypotheses and guide experimental designs.

**III. Clarifying the rigor of our hypothesis tests and scope of our inferences on drivers of infection duration.**  We agree with the reviewers that our original proposal was insufficiently clear on alternative hypotheses and generalizability of our inferences to other host-parasite systems, including human helminthiasis. In the revised application, we provide a fuller explanation of our hypotheses – not just the threshold-driven Allee effect hypothesis, using the mechanistic model to identify general patterns that are expected under each hypothesis. This helps justify fine-scale dosing in our experiments and clarifies that our goal is mechanistic understanding. We also address generalizability of our inferences in several ways. For example, we have clarified that: A) we expect that the processes by which immune signalling determines infection duration will apply to other host-parasite systems, generating testable hypotheses for cross-regulation among T-helper subsets in those contexts; and B) the differences in the rate of worm clearance among individual hosts within a genotype are an explicit focus of our work, and we contend that we can explain these differences using the same dynamical “rules” that explain variation among mouse genotypes, or across environments. Finally, we clarify that rewilding (and even rewilded transplant) makes T cells and neutrophils of mice better model adult mammals, including humans, AND increases duration of *Trichuris muris* infection. We argue that by incorporating diverse microbiota and trickle infections, we will make *T. muris* a better model for the chronic helminthiasis that afflicts half a billion people.

**In addition, we revised to address many further suggestions of the reviewers, including:** specifying greater experimental details throughout; decoupling interdependency of the aims; using knockouts rather than monoclonal antibodies to increase reproducibility of our immune manipulations; referring to strains rather than genotypes when discussing mice to avoid confusion; sensitivity to cytokine; better defining the growth of parasite biomass; and clarifying that Graham has a trainee in house to begin the work.

We thank the reviewers for their thoughtful critical feedback. We hope that they agree that these revisions have clarified the novelty and improved the rigor and impact of our proposal.