Personal statement: I am a perfect fit for this project because it leverages my past experience yet provides training that matches my career goals. I hope to lead a lab that uses massively parallel assays and modeling to understand how sequence information encodes phenotype. I aim to study fundamental problems with an eye for impactful applications. My proposed project aligns perfectly with my goals, allowing me to explore new applications of these techniques through fundamental questions with deep relevance for human health. The central question I ask in this proposal is, how does the sequence of an RNA molecule create anti-correlation between splicing decisions. I will develop massively parallel splicing assays to identify sequences essential for mutually exclusive splicing and characterize them with targeted experiments and modeling. My model system will be exons 9 and 10 in pyruvate kinase M, a splicing switch that drives the Warburg effect in cancer, however the tools I develop will be useful for understanding correlated splicing in many proteins and disease systems. This project perfectly leverages skills I built through my time in graduate school. During my Ph.D., I performed massively parallel growth assays to identify genes essential for CO_2 concentration in a chemoautotroph and measured their phenotypes across CO_2 concentrations. I then illuminated mechanistic details with biochemical and genetic experiments.[1,2] In a second currently ongoing project, I used a massively parallel growth assays and modeling to map the fitness landscape of dihydrofolate reductase and design novel variants. In collaboration with the Doudna lab, I demonstrated my skill in biochemistry by showing zinc binding in the newly discovered CasX,[3] and applied my modeling, data analysis, and statistical expertise to signal amplification in CRISPR diagnostics.[4] These experiences prepared me to use massively parallel assays, genetic and biochemical experiments, and modeling to characterize splicing. My proposed project will allow me to further expand my skills and explore applications to RNA biology, in the human-cell context, and using long read sequencing, skills that will aid me in my independent research career. Further, this experience will allow me to strengthen my modeling abilities by working with expert teams in the Kinney lab and the Simons Center for Quantitative Biology. Finally, at Cold Spring Harbor I will have access to a wide variety of training resources including attending the on campus meetings like Eukaryotic RNA processing and the Probabilistic Modeling in Genomics.

[1] John J Desmarais et al. "DABs are inorganic carbon pumps found throughout prokaryotic phyla". en. In: *Nat Microbiol* 4.12 (Dec. 2019), pp. 2204–2215. ISSN: 2058-5276. DOI: 10.1038/s41564-019-0520-8.

[2] Avi I Flamholz et al. "Trajectories for the evolution of bacterial CO_2-concentrating mechanisms". In: *Proceedings of the National Academy of Sciences* 119.49 (2022), e2210539119. DOI: 10.1073/pnas.2210539119.

[3] Jun-Jie Liu et al. "CasX enzymes comprise a distinct family of RNA-guided genome editors". en. In: *Nature* (Feb. 2019), p. 1. ISSN: 0028-0836. DOI: 10.1038/s41586-019-0908-x.

[4] Tina Y Liu et al. "Accelerated RNA detection using tandem CRISPR nucleases". en. In: *Nat. Chem. Biol.* (Aug. 2021), pp. 1–7. ISSN: 1552-4450. DOI: 10.1101/2021.03.19.21253328.