Research Proposal

In general, the more academic experience an applicant has, the more this should be reflected in the proposal. (not to exceed two pages, double-spaced)

* Describe clearly your chosen area of study and the research issue that interests you.

* Explain why your chosen institution is especially suited to your field of study and to the type of work you plan to undertake.

* Explain the relevancy of the courses you plan to take and how they relate to your plan of study.

* If possible, describe the research methods and theoretical framework you plan to use.

* Relate your proposed research to a larger academic community and society as a whole. Explain why your study will be useful.

Current methods to study a complex tissue such as a cancer tumor use homogeneous cell lines, which does not represent the reality of a tumor: a chaotic mix of different, interacting cell types. I want to understand this chaotic mix by studying the differences between single cells of a primary cancer tissue. This work will lay the foundation for creating more realistic research models of cancers, such as mixes of different clonal types, to represent more closely the true tumor composition.

Chronic lymphocytic leukemia (CLL) is the most common adult B-cell leukemia in Western countries, and approximately 10% of affected individuals have a mutation in the spliceosomal subunit SF3B1 [1,12]. It is likely that there are more splicing-related mutations as known oncogenic splicing factors in other cancers [4,5]. The SF3B1 mutations are associated with increased disease survival and poor prognosis. I want to study how SF3B1 is differentially mutated between individual cells, and how this affects alternative splicing mechanisms. I will work with Profs. Gene Yeo and Trey Ideker here at UC-San Diego (UCSD). Yeo is an expert in alternative splicing and [has] a single-cell sorting device which places cells into individual wells of a 96-well plate, while Ideker pioneered biological network analysis. We could use RNA-Sequencing (RNA-Seq) to study both mutations and alternative splicing using an assembly-based read mapping tool [8], and compare to a reference sequence, however, this has two major limitations. First, the seed sequence used in the algorithm is a minimum of 25 nucleotides (nt), so microRNAs (miRNAs), 20-22 nt key negative regulators of mRNA in CLL [9,10,13], are missed. Second, assembling RNA without comparing to DNA would ignore RNA-editing mechanisms, but CLL cells are known to express AID, a potential RNA-editing enzyme [6,7].

To fully understand the gene expression story, I propose to simultaneously perform both RNA- and DNA-Seq (R+D-Seq) on individual cells of a CLL primary tumor. This is especially important in cancer, composed of heterogeneous cells which may each have their own individual genomic chaos affecting which transcripts they can produce. Groups has extracted RNA and DNA from small samples but not in a high throughput manner, and not with a single cell [2,3]. Performing R+D-Seq on individual cells of primary CLL tumors would reveal the effects of alternative splicing (AS), RNA-editing, and miRNAs, and we could infer their contribution to the whole cancer tissue. This study would pave the way for future understanding of heterogeneity within other tissues, not limited to cancer, and the development of R+D-Seq would deepen the field of genomics by uncovering subtle relationships between RNA and DNA not detectable by observing one sequence alone.

Previous Research

Describe any research in which you have participated. You may have undertaken research as part of your coursework or outside of class in an internship or summer research program.

If you are currently engaged in research, explain the methods used and the expected results of your work.

Personal Statement

*** the applicant's capacity to respond in pedagogically productive ways to the learning needs of students from diverse backgrounds**

*** the applicant's sustained personal engagement with communities that are underrepresented in the academy and ability to bring this asset to learning, teaching and scholarship at the college or university level**

*** the applicant's likelihood of using the diversity of human experience as an educational resource in teaching and scholarship**