**ABSTRACT**

Diffuse Large B Cell Lymphoma (DLBCL), the most common B cell non-Hodgkin lymphoma, is a complex and aggressive disease that originates from the malignant transformation of germinal center (GC) B cells. Despite significant advances in the genetics and biology of these cancers, including seminal contributions by the Unit Director, DLBCL remains an unmet clinical need. The general goal of the research program in the Pasqualucci (Unit Director) and Dalla-Favera lab is aimed to address this gap by applying a combination of genomic approaches, epigenetic tools, and genetically engineered mouse models to identify and functionally characterize the genetic alterations associated with these tumors, with emphasis on i) the role of mutations in histone/chromatin modifier genes, representing the most common genetic alteration associated with Fl and DLBCL (parent R01-CAXXXXXX (date)(Pasqualucci et al., *Nature* 2011, PMID: 21390126; *Nature Genetics* 2011, PMID: 21804550; Zhang et al., *Cancer Discovery* 2017, PMID: 28069569; Meyer et al., *Immunity* 2019, PMID: 31519498); ii) the mechanisms and consequences of super-enhancer dysregulation caused by aberrant somatic hypermutation (Bal et al., *Nature* 2022, PMID: 35794478); and iii) the identification of transcription networks/molecular mechanisms controlling the biology of GC B cells and perturbed during the malignant transformation process, as a mean to stratify lymphoma patients into subtypes of pathogenetic and clinical relevance (Holmes et al., *JEM* 2020, PMID: 32603407). This work heavily relies on the development and use of multiple programming languages, including Python, R, and Java, as well as widely used bioinformatics packages, including STAR, Seurat, DESeq and 10X and Illumina tools, for the analysis of large-scale experimental data at bulk and single cell level, that have been mastered by the applicant over the past 10 years as an Associate Research Scientist in the Unit Director’s lab. The key role of the applicant in the Unit Director’s program is documented by the number of high-impact publications and NCI-funded grants to which he has contributed. This application will provide stable salary support for the candidate and thus allow him to continue to bring his unique bioinformatics expertise in the design and integration of tools for the analysis, visualization and interpretation of high-throughput transcriptomic, genomic, and epigenomic data. The goals of the proposed research plan are in line with the parent R01 but also bring new concepts and support to other areas of investigation within and outside the Unit Director’s lab, which are focused on understanding the pathogenesis of B cell malignancies. As such, sustain the research program of the Unit Director and more generally the biomedical enterprise.