1. INTRODUCTION

1.1. Project Background

The massive unfulfilled clinical need for liver cancer treatment has been persistent due to a poor representation of patients' highly heterogeneous tumors in pre-clinical research. A more patient-specific approach is necessary by providing drug panels on patient-derived tumor cells to generate clinically relevant treatment options for hepatocellular carcinoma (HCC) patients in Asia-Pacific. A patient-specific diagnostic and predictive platform serves as an artificial intelligence (AI) database constructed by the laboratory's project, involves 'teaching' the AI system to construct a suitable tailored drug treatment based on the patient's HCC genomic and proteomic profile. A collective data of drug screening result from several hundreds patient-derived samples serve as the program's point of reference. Numerous patients' samples exhibit certain drug resistance triggered by a particular molecular aberration which are yet to be known. To further investigate the underlying mechanisms of drug resistance observed in patient's tumors, cancer cell lines are used as models for the drug response prediction. An appropriate biological model which consist of spheroid is paramount to represent the heterogeneity of the primary liver tumor is used.

Certain molecular signatures were observed in cancer stem-like subpopulation of the heterogeneous HCC, which involve aberrant signaling that could lead to HCC's oncogenic properties. The aberrant signaling commonly associated with HCC progression is the NFkB pathway, being directly affiliated to the chronic inflammatory etiology the cancer are derived from. Being able to regain proper regulation of NFkB hyperactivation in HCCs is the endeavour of many therapeutic researches, yet the complexity of NFkB regulation still remains a conundrum. One molecule of interest is a lncRNA, loc[redacted], identified by Prof. Vinay Tergaongkar's laboratory IMCB A*STAR as NFKB's nuclear activity regulator are found to be highly upregulated in the events of high inflammatory conditions and within HCC CSC. The lncRNA, by converging with an RNA helicase, able to inhibit a protein phosphatase from dephosphorylate and inactivate p65's transcription activity. The influence of the lncRNA on NFkB temporal activation and gene expression holds a potential to be a therapeutic target.

This study further explores the influence of the loc [redacted] towards CSC attributes which are primarily responsible for drug resistance in primary tumors.

1.2. Problem Formulation

The previous research done by Prof. Vinay Tergaongkar's laboratory have managed to characterize an evolutionary conserved, NFkB-specific lncRNA which functions by coordinating the activation of NFkB transcriptional activity through covalent modification of the p65 subunit that are implicated in chromatin remodeling and gene expression. However, the extent to which this loc [redacted] are able to influence the phenotype of cancer cells are not yet explored. The analysis on NFkB-dependent cellular attributes and phenotype is vital to determine its significance of the leverage this lncRNA over NFkB signaling.

By having a certain degree of control over NFkB signaling, the loc [redacted] may account for the influence on the stemness attributes observed in HCC tumors. Cancer stemness, resulted from CSC, are known to be maintained by chronic inflammatory conditions in which NFkB acts is the key mediator. Unlocking the potential impact loc [redacted] on HCC stemness through NFkB signaling may reveal a solution to the persisting stemness-dependent chemoresistance observed in HCCs.

1.3. Research Objectives

- Creating a suitable biological model that could represent HCC stemness.
- Observe the influence of loc [redacted] on NFkB basal activity as a predeterminant to stimulated canonical signaling of NFkB.
- Associate the NFkB target gene expression to HCC stemness attributes.
- Analyse the implication of altered stemness character by the modified NFkB activity towards its response to HCC anti-cancer drugs.