CHAPTER 1: INTRODUCTION

1.1. Background

The immune system's role toward the biology of cancer was a highly debated topic only a few decades ago. Immunosurveillance – the notion that the immune system actively seeks out and eliminate neoplastic cells – was proposed by Burnet in 1970, and this hypothesis was challenged in the following few decades up until the 1990s when the researchers already had sufficient technologies to properly investigate the hypothesis (Dunn et al., 2004). After we have confirmed that our immune system components do serve as tumour suppressors, and we have seen considerable progress in the field of cancer immunology since then (Smyth, Dunn, & Schreiber, 2006). We have taken this knowledge to our advantage in our fight against cancer that we developed a new branch of cancer therapy — immunotherapy. Today, we have various immunotherapeutic strategies, including immune checkpoint inhibitors, bispecific antibody, chimeric antigen receptor (CAR) T-cell, and cancer vaccination (Liu & Guo, 2018).

That said, immunotherapy is still facing its major hurdle: resistance (Restifo, Smyth, & Snyder, 2016). A long-term clinical study of anti-CTLA4 ipilimumab showed a sustained response only in a subset of patients (Schadendorf et al., 2015). In CD19 CAR T-cell therapy, around 30-60% of acute lymphoblastic leukaemia (ALL) patients have their disease relapsed despite the high complete remission (CR) rate (Xu et al., 2019). Blinatumomab, a bispecific T cell engager (BiTE) targeting CD19, was shown to induce CR in less than half of the patients in a phase II study (Liu et al., 2019). These shreds of evidence showed that resistance to therapies plagued many, if not all, of our battlefronts of immunotherapeutic strategies.

Perhaps the resistance toward immunotherapies is more apparent in solid cancers due to the microenvironment that can induce immunosuppression through various mechanisms (Tokarew et al.,

2018). One of the ways microenvironment can become immunosuppressive is because of the decreased oxygen availability – hypoxia. Among its varied impacts, hypoxia has been demonstrated to alter the behaviour of some components of the immune system, such as CD8+ T cell (Caldwell et al., 2001). These changes in the behaviour of the immune system might come from the alteration of gene expression that the immune cells could undergo under hypoxic condition. The main way of how hypoxia can alter gene expression is through the activation of transcription factors, such as HIF1α, which becomes stabilised during hypoxia to increase the expression of hypoxia-response genes – notably, these genes include vascular endothelial growth factor (*VEGF*) gene, which induces angiogenesis (Melstrom et al., 2011). Beyond that, however, hypoxia has also been shown to induce changes in epigenetic regulation which would also result in the alteration of gene expression (Camuzi et al., 2019). Therefore, it is an exciting prospect to explore whether epigenetic changes under hypoxia contributes to hypoxia-induced immune suppression.

In this project, we would like to assess the potential of targeting epigenetic, particularly histone regulators, to reverse the suppression of CD8+ T cell under hypoxia. We were also going to study how hypoxia affects the interaction between CD8+ T cell and cancer cells. As the cancer model, triple-breast cancer (TNBC) cells were chosen as it has been demonstrated to be more hypoxic compared to other breast cancer subtypes. TNBC is a subtype of breast cancer that lacks the molecular markers that, compared to other breast cancer subtypes, could be potential therapeutic targets (Sporikova et al., 2018). Recently, the use of atezolizumab, an immune checkpoint inhibitor, has been approved by United States' Food and Drug Administration (FDA) for a specific subset of TNBC patients (Cyprian et al., 2019). Given their potential ability to reverse hypoxia-induced immune suppression, epigenetic treatments might be able to synergise and enhance immunotherapy, such as immune checkpoint inhibitor.

1.2. Research Objectives

This project aims to study the activity of CD8+ T cells under hypoxic condition – on the expression of CD8+ T cell effectors as well as the activity of the CD8+ T cells on TNBC cell lines under hypoxia. We also tested several epigenetic drugs on its effect toward restoring the activity of the CD8+ T cell.