CHAPTER I

INTRODUCTION

Cancer is a group of diseases that are different and distinct, with more than 277 types of cancer that are currently known, where abnormal cells grow uncontrollably and invade other tissues (Mathur, Nain, & Sharma, 2015; Mitra, Ganguli, Chakrabarti, 2018; Hassanpour & Dehghani, 2017). Cancer was the number 1 cause of death worldwide in 2020 with an estimated 10 million deaths, with the majority (70%) coming from LMIC countries (World Health Organization, 2021; List & Connor, 2020). In Indonesia, there have been more than 390 thousand new cancer cases and more than 230 thousand cancer-related deaths in 2020 (Ferlay et al., 2020). In high-income countries, cancer has also surpassed CVD in regards to the number of deaths it has caused (Mahase, 2019). However, the mortality rate of cancer in LMIC, which includes Indonesia, is more likely to be associated with poorer access to healthcare rather than the risk factors, as high-income countries have higher prevalence in high-income countries (Mahase, 2019). Therefore, it is important to search for a treatment or prevention of cancer to minimize the cancer mortality number.

Surgery, Chemotherapy, and Radiotherapy are the currently widely used treatments for cancer (Abbas & Rehman, 2018). However, the advancement in cancer therapy has also enabled new therapies to emerge and offer patients another type of treatment, including hormone-based therapy, stem cell therapies, angiogenesis inhibitors, gene therapy, thermal ablation, nanomedicine, targeted therapy, and immunotherapy (Abbas & Rehman, 2018; Pucci, Martinelli, & Ciofani, 2019). Among them, immunotherapy is currently viewed as a very promising therapy for cancer, offering a more targeted and specific treatment compared to conventional treatments (Taefehshokr et al., 2020). Cancer immunotherapy works by utilizing the immune system to exhibit anti-tumor responses, and has been shown to improve patient prognosis (Papaioannou et al., 2016; Kruger et al., 2019). There are currently many types of cancer immunotherapy, including checkpoint inhibitors, cellular immunotherapy (e.g. CAR T-cells), naked and bispecific monoclonal antibodies, combinational therapy, non-specific immunotherapy (e.g. uses of interferons and interleukins in therapy), oncolytic

viruses, and cancer cell vaccine (Velcheti & Schalper, 2016; Kruger et al., 2019; Bondhopadhyay et al., 2020). The current immunotherapy intervention works either by targeting the immune evasion mechanism (e.g. checkpoint inhibitors) or stimulating the immunological response (e.g. cancer vaccines) (Velcheti & Schalper, 2016). Among them, therapeutic cancer vaccines have been gaining attention the past few decades due to its ability to induce immunological memory response, high specificity, and low toxicity (Saxena et al., 2021; Emens, 2008).

Cancer vaccines can be grouped based on the materials it was derived, including cells, virus, protein, bacteria, peptide, and also genetic material (Lopes, Vandermeulen, & Préat, 2019). It can be used as a treatment or prevention of cancer (Stephens, Burgess-Brown, & Jiang, 2021). One of the examples of cancer vaccines that has been used is the HPV vaccine that has been proven to be effective for prevention of cervical cancer (Kjaer et al., 2021). This study will be focusing on peptide-based vaccines. This vaccine is able to activate and increase TAA-specific T cell expansion (Kumai et al., 2017). Peptide-based vaccines have several advantages compared to other vaccines. Peptide-based vaccines with CTL and HTL cell epitopes, which are important in eliciting anti-tumor activity, have low toxicity, easier to produce, simpler to administer, has a low risk of inducing antigen-induced anaphylaxis, and is flexible in changing the antigen (Lopes, Vandermeulen, & Préat, 2019; Kumai et al., 2017). In addition, unlike adoptive cell transfer (ACT) therapies, no GLP cell-processing would be needed in peptide-based vaccines, which make it more cost effective (Kumai et al., 2017). However, peptide-based vaccines are restricted to people who have certain HLA alleles and careful formulation of the vaccine is needed to ensure the peptides are immunogenic (Lopes, Vandermeulen, & Préat, 2019; Kumai et al., 2017). Therefore, the vaccine in this study would be designed to be restricted to HLA alleles commonly found in the Indonesian population.

The TAA used in this study would be MAGE-A10 and NY-ESO-1, which are classified as cancer testis antigen (CTA). CTA expression is typically absent in adult somatic cells, except for testicular germ cells, but can be found in various cancer cells; therefore, it is considered an ideal immunotherapeutic target (Scanlan et al., 2002; Wei et al., 2019; Gjerstorff, Andersen, & Ditzel, 2015). NY-ESO-1 is a

protein encoded by CTAG1B with little known biological function (Thomas et al., 2018). However, NY-ESO-1 presence has been observed in various tumor, including prostate cancer, neuroblastoma, sarcoma, melanoma, lung, breast, ovarian cancer, and many others; It is also reportedly able to induce adaptive immune response and be recognized by CTLs (Wei et al., 2019; Scanlan et al., 2002). MAGE-A10 is a part of MAGE-A family whose function is also unclear; however, some MAGE-A family members are known to be involved in p53 dysregulation (Zajac, 2017). MAGE-A10 has been reported to be highly immunogenic and overexpressed in various cancer cells, including skin, gallbladder, lung, urothelial, TNBC, and stomach cancers (Schultz-Thater et al., 2011; Badovinac Črnjević et al., 2012). Therefore, the use of both NY-ESO-1 and MAGE-A10 in this study might be able to elicit antitumor response to many types of cancer.

This study aims to design a peptide-based vaccine derived from NY-ESO-1 and MAGE-A10 for the Indonesian population against cancer. The study would be done *in silico*, involving vaccine construction from CD8 and CD4 T cell-reactive epitopes, testing for allergenicity, antigenicity, physicochemical properties, testing its population coverage, running simulation of immune system reaction towards the vaccine, and docking the vaccine to TLR4. The vaccine would also be checked for its cross-reactivity and whether the HLA molecules would be able to present the epitopes.