CHAPTER 1: INTRODUCTION

1.1 Project Background

Cancer caused many deaths worldwide thus leads to hindrance in increasing the life expectancy of people around the world (Sung et al., 2021). Approximately, there were nineteen million incidences and nearly ten million deaths caused by cancer in 2020 alone (Sung et al., 2021). And currently, surpassing lung cancer, breast cancer in women has become the most frequently diagnosed to have cancer, estimating around 2.3 million new cases around the world and accounts for 6.9% of deaths caused by cancer around the world (Sung et al., 2021). According to Global Cancer Observatory (2021), in Indonesia, breast cancer holds the highest occurrence as opposed to other cancers and causes approximately 9.6% mortality.

There are several therapies that are used to treat breast cancer. Those therapies are surgery, radiotherapy, chemotherapy, and hormone therapy (Nounou et al., 2015). However, those treatments have limitations. For example, surgery is only suitable for non-metastatic breast cancer (Nounou et al., 2015). While radiotherapy may increase the chance of developing secondary malignancy (Dracham et al., 2018). It also may cause decreased sensation in the treated area like the breast tissue and also cause itching, redness and soreness (Nounou et al., 2015). Chemotherapy or cytotoxic drugs, on the other hand, can cause adverse effects including nausea, vomiting, and hair loss (Altun & Sonkaya, 2018).

Currently, the cancer vaccine has drawn the attention of many researchers due to its high specificity and lower toxicity (Emens, 2008). In addition, it also provides durable immune memory (Dillon, 2017). There are several types of cancer vaccines, however, in this study, the focus is on a peptide-based vaccine. The effectiveness of the vaccine strongly depends on the nature of the antigen (Saxena et al., 2021). The antigens used can be self-antigens, differentiation antigens, overexpressed antigens, and non-self antigens (Saxena et al., 2021).

Mucin 1 (MUC-1) is a glycoprotein that protects the epithelial lining ducts in multiple organs including the mammary gland and is one of the examples of overexpressed antigens

(Kufe,2012). It was found that MUC-1 is abundant in more than 90% of breast cancer (Kufe,2012). Similarly to MUC-1, metalloproteinase 9 (MMP-9) is overexpressed in breast cancer cells than in healthy breast cancer cells (Huang, 2018). MMP-9 has a proteolytic activity that aids the deconstruction of the extracellular matrix (ECM) and basement membrane (Huang, 2018). Since both MUC-1 and MMP-9 are abundant in breast cancer they can be the candidate for the antigens for the vaccine development.

Although, there have been studies about breast cancer vaccines (Clifton et al., 2020; de Paula Peres et al., 2015; Liu et al., 2020). Previous studies of cancer vaccines were not specifically designed for the predominant HLA alleles in the Indonesian population. Therefore, to reduce both the health and economic burden of breast cancer in Indonesia, developing a vaccine might be the solution to overcome this problem. Using the immunoinformatics approach, a cancer vaccine can be developed. This approach may accelerate the development of the cancer vaccine and its translation into clinical practice (De Groot et al., 2020).

1.2 Objectives

The study aims to find peptides from Mucin 1 (MUC-1) and Metalloproteinase 9 (MMP-9) that are presented by predominant HLA alleles of the Indonesian population using immunoinformatics tools and to construct a multi-epitope peptide-based vaccine that target MUC-1 and MMP-9 for breast cancer treatment.

1.3 Research Scope

The scope of the research includes :

- Sequence retrieval of MUC-1 and MMP-9 sequence from the Uniprot database.
- Cytotoxic T-cell (CTL) and helper T cell (HTL) epitopes prediction using NetCTLpan and NetMHCpanII, respectively.
- B cell epitopes prediction of MUC-1 and MMP-9 using IEDB B cell epitopes prediction tools

- Immunogenicity prediction using IEDB immunogenicity prediction tool
- IFNγ induction capability prediction using IFNepitope server
- Epitopes clusterization using IEDB clusterization tool
- Designing a vaccine construct
- Antigenicity evaluation of vaccine the construct using ANTIGENpro and VaxiJen webserver
- Allergenicity evaluation of vaccine the construct using AllerTop webserver
- Physicochemical characteristic evaluation of the vaccine construct using ProtParam webserver
- Solubility evaluation of the vaccine construct using SOLpro
- Toxicity evaluation of vaccine construct using ToxinPred
- Population coverage evaluation of the vaccine construct using IEDB population coverage prediction tool
- Cross-reactivity against human proteome using NCBI BlastProtein
- Cross-reactivity against human microbiome using PBIT web server
- Immune response simulation of the vaccine construct using C-ImmSim
- Molecular docking of TLR4 and vaccine construct
- Molecular docking analysis of ^{1040}SFFFLSFHI^{1049} binding to HLA-A*24:07 and HLA-A*24:02