CHAPTER I: INTRODUCTION

1.1 Background

The SARS-CoV-2 has been subjected to mutations resulting in the appearance of various new variants of SARS-CoV-2 including the VOC which are alpha, beta, gamma, delta and omicron variants. Study by Gómez, Perdiguero & Esteban (2021) stated that the new variants of concerns have several characteristics in common such as increased transmissibility, high amount of mutation on the spike (S) protein, particularly in the RBD and NTD. This will increase the affinity of S RBD for the ACE2 receptor resulting in higher infection rates. Study also showed that the VOC showed signs of increased re-infection frequencies, enhanced virulence, and increased resistance towards antibodies from vaccination.

T-cell is involved in viral infection control and providing immunological memory that is important for lasting protection against the virus. T cells can differentiate into CD4+ T helper cells that aid B cells with producing antibodies and CD8+ cytotoxic T cells. To develop vaccine and immunotherapies, identifying and understanding the exact T-cell epitope is crucial (Nelde et al., 2020). Studies have shown that SARS-CoV-2-specific T-cells related with disease development, and individuals with high T-cell responses to protein in SARS-CoV-2 (S protein, M protein, and N protein) do not develop COVID-19, unlike individuals with low T-cell response. This indicates that T-cell involvement is a strong factor for predicting whether a patient will develop mild or severe symptoms and also involved in protection against subsequent infection (Meyers et al., 2021).

The study of T-cell cross-reactivity among different variants of concern is still limited and this project aims to assist the lack of information regarding the specific mutation in T-cell epitopes among variants and analyze its impact on binding affinity and possibly the chance of cross-reactivity. There is a possibility that survivors from the first SARS-CoV-2 wave will still be affected by the second wave. If

the T-cell epitope changes drastically from the parent variant, it is possible that the immune system capability to recognize the other SARS-CoV-2 variants may be greatly reduced.

This project will follow the T-cell epitope changes from wild-type SARS-CoV-2 (Wuhan-Hu-1) into Alpha, Beta, Gamma, and Delta variants. Additionally, the epitope changes will be analyzed whether it would result in no binder or decreased binding with multiple HLA alleles that have allele frequency equal or higher than 5% in the Indonesian population. As a final step, a phylogenetic tree based on the T-cell epitope of each variant will be constructed to analyze, map and trace the changes on the T-cell epitopes of the different variants.

1.2 Research Question

- How is the evolutionary relationship between the epitopes of Wuhan-Hu-1 with other SARS-CoV-2 variants?
- How do the epitopes originating from S protein of Wuhan-Hu-1 differ from those originating from other variants?
- Is there any new unrecognizable peptide resulting from the occurrence of variants?
- How much of the T cell epitopes conserved from Wuhan-1 are present in the new variants?
- Does the mutation occuring in the epitopes cause a decrease in binding capacity with HLA alleles?

1.3 Objectives

The objective of the research is to:

- Investigate the T-cell epitope changes from Wuhan-1 SARS-CoV-2 into Alpha, Beta, Gamma, Delta, and Omicron and its effect on the immunogenicity and binding affinity with HLA alleles among the Indonesian population.

- Map and trace the changes of the T-cell epitopes among different variants by means of phylogenetic analyses.

1.4 Research Scope

The scope of work of this ToR is:

- Gathering the protein sequences from the SARS-CoV-2 ancestral sequence (Wuhan Hu-1) and various patients that have been infected by different types of COVID-19 variants (Alpha, Beta, Gamma, Delta, and Omicron) from GISAID.
- Predict T-cell epitopes from SARS-CoV-2 that will be presented by HLA alleles found in the Indonesian population with at least 5% allele frequency.
- Investigate the epitope changes of each variants and find the conserved regions
- Analyze the impact of peptide changes to the binding of human HLA alleles
- Phylogenetic tree analysis based on T-cell epitope