# iscovery_from_Isocitrate_Dehydrogenase_Type_1_R132H_Epitopes.pdf

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# In Silico Research in Glioma Vaccine Discovery from Isocitrate Dehydrogenase Type 1 (R132H) Epitopes

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## Abstract

*Glioma is a primary malignant brain tumor, which is often detected using the mutation of isocitrate dehydrogenase type 1 (IDH1) at the R132H position. Several studies have also reported the use of mutated IDH1 (R132H) specific immunogenic epitopes as vaccines against this tumor. Therefore, this study aimed to determine the high-affinity epitopes of IDH1 (R132H) as a plausible candidate of preventive and curative glioma vaccines and to predict the stability of epitope-receptor complex through molecular dynamics simulation. The binding affinity of epitopes for preventing and treating glioma were predicted by docking epitope to major histocompatibility complexes class II (MHC II) and ephrin type-A receptor 3 (EphA3), respectively, using Dock version 6.7. This study used the rigid body docking method, where the samples were treated in their compact state. The highest binding affinity for MHC II was exhibited by epitope 42, as indicated by a grid score of -62.73 kcal/mol. Meanwhile, epitope 54, with a grid score of -55.56 kcal/mol, had the highest binding affinity for the EphA3 receptor. The results showed that the protein conformation in the 42-MHC II epitope complex changed significantly in molecular dynamics simulations using GROMACS version 5.0.6 at 300 K for 25 ns with RMSD > 3 Å, while epitope 54-EphA3 complex was stable from the beginning up to 15.29 ns. Based on these findings, the best candidates for prophylactic and curative glioma vaccination were epitope 42 and 54, respectively.*

***Keywords:*** epitope, glioma, IDH1 (R132H), in silico, vaccines

## 1. Introduction

Brain tumors account for approximately 85-90% of all central nervous system cancers, with glioma being the most prevalent type (Colopi *et al.*, 2023). Furthermore, glioma is a malignant primary brain tumor that originates from glial cells (Delgado-Martín and Medina, 2020). In recent years, scientists have

made significant efforts to identify the genetic basis of this condition. This information is expected to help in the development of more effective therapies for patients with a poor prognosis (Ko and Brody, 2021; Choi *et al*., 2023).

The body relies on the enzyme isocitrate dehydrogenase 1 (IDH1) to produce adenosine triphosphate (ATP) through the citric acid cycle. However, mutations in IDH1 can cause the production of an oncometabolite, namely 2-hydroxyglutarate (Kandel-Massler *et al*., 2019; Tangella *et al*., 2023). Although a somatic mutation in codon 132 of the IDH1 gene on locus chromosome 2q33 has been identified in a few glioblastomas cases, it has been found in several low-grade glioma (Testa *et al*., 2020; Ahsan, 2022; Hasanzadeh and Niknejad, 2021; Senhaji *et al*., 2022). Among the six different mutations of IDH1, the variation at R132H, in which arginine transforms into histidine is the most frequent (> 85%) (Arita *et al*., 2015; Matteo *et al*., 2017; Franceschi *et al*., 2021; Shayanfar *et al*., 2023). IDH1 (R132H) can be a biomarker for the presence of glioma ( Mirchia and Richardson, 2020; Fujita *et al*., 2022).

IDH1 (R132H) has been reported to have potential as a tumor-specific neoantigen and is a promising target for immunotherapy. The enzyme contains immunogenic epitopes that are suitable for vaccination (Platten *et al*., 2021; Yu *et al*., 2022). Cancer vaccines can be divided into two major categories based on their intended usage, namely prophylactic and therapeutic. Prophylactic vaccines are often used to prevent cancer, while therapeutic variants are applied to treat the condition and build body resistance (Kaczmarek *et al*., 2023; Zhang *et al*., 2023). Furthermore, peptide-based vaccines can be produced by generating antigenic peptides from proteins produced by the tumor cells of interest. It is also important to predict whether the peptides are likely to bind to specific MHC molecules in humans to ensure the efficacy of the therapy developed (Abd-Aziz and Poh, 2022).

The epitopes of IDH1 (R132H) are present in major histocompatibility complexes class II (MHC II) and stimulate mutation-specific $CD4^+$ T helper-1 (TH1) cells. In glioma patients with R132H mutations, $CD4^+$ T helper-1 (TH1) and spontaneous antibodies recognize IDH1 (R132H) preferentially (Bunse *et al*., 2022). Since all tumor cell surfaces exhibit the enzyme in its R132H form, vaccines can alert the immune system of humans to its presence without causing harm to the healthy cells (Kaczmarek *et al*., 2023; Liu *et al*., 2023). Large quantities of the ephrin type-A receptor 3 (EphA3) are expressed in gliomas and mesenchymal subtypes of glioblastoma. EphA3 expression is considerably higher during the early stages of tumor development, where cell

differentiation has not yet occurred. EphA3 actively contributes to the maintenance of undifferentiated tumor cells. Furthermore, therapeutic targeting of the EphA3 receptor could be applicable to these tumors (Zheng *et al*., 2020; Baumgartner *et al*., 2021; Arora *et al*., 2023)

Homology modeling has been carried out to analyze 91 epitopes of IDH1 (R132H) that show potential as cancer antigens based on antigenicity prediction result with a threshold limit of ≥ 0.4 using VaxiJen, followed by validation and refinement of the structures. These epitopes have been predicted to bind strongly to MHC II allele HLA-DRB10101 because they have an $IC_{50}$ value of less than 50 nM (Yeni and Tjahjono, 2017). Several studies have explored the use of computational methods in identifying compounds. The use of in silico-based methods to predict epitopes for producing peptide vaccines designed rationally has been reported to improve the efficacy of vaccination (Sunita *et al*., 2020; Rawal *et al*., 2021; Kalita and Tripathi, 2022; Soleymani *et al*., 2022; Guarra and Colombo, 2023).

Docking studies have been instrumental in computer-aided drug design (CADD) and are often used for virtual screening or lead optimization in drug screening. Protein-ligand or protein-protein docking studies can be used to predict the direction of a ligand when it is bound to a protein receptor or enzyme (Siebenmorgen and Zacharias, 2020; Supandi *et al*., 2021; Yeni *et al*., 2020, 2021). Furthermore, molecular dynamics simulation is a method that is often utilized to comprehend the physical underpinnings of the structure and function of biological macromolecules. During simulation, proteins have a dynamic model, in which internal motions and conformational changes are crucial to their function (Guterres and Im, 2020; Hashemzadeh *et al*., 2020; Lazim *et al*., 2020; Salo-Ahen *et al*., 2021; Rampogu *et al*., 2022) The root-mean-square deviation (RMSD) graph initially exhibits a steep slope for the first few nanoseconds (ns) and then stabilizes around a constant average value for the rest of the process. The root-mean-square fluctuations (RMSF) graph can be used to illustrate the magnitude of fluctuations of every atom or residue in the protein (Abraham *et al*., 2023). Based on these findings, this study aims to determine the high-affinity epitopes of IDH1 (R132H) as a plausible candidate of preventive and curative glioma vaccines and to predict the stability of epitope-receptor complex. Docking and molecular dynamics simulation methods were utilized to determine the affinity of samples against MHC II and EphA3 receptors to predict the preventative and curative activities, respectively.

## 2. Methodology

### 2.1 Docking Studies

The docking study was carried out using Dock version 6.7 (Lang *et al*., 2015) based on the method proposed in a previous report (Lang *et al*., 2015). IDH1 (R132H) epitopes (Table 1) were docked with MHC II HLA DRB1 0101 (PDB: 1AQD) and the EphA3 (PDB: 4TWO) receptor, which had been separated with native ligands using Discovery Studio version 16.1.0.15350. Furthermore, the structure of the receptors was obtained from the Protein Data Bank (Burley *et al*., 2022). The native ligand for MHC II and EphA3 was A2 peptide and compound 164, respectively. The docking method used in this study was rigid body docking, which was proposed by previous studies (Chen *et al*., 2020; Desta *et al*., 2020; Tao *et al*., 2020). Redocking between the receptors and their native ligand was performed before epitopes were docked to obtain RMSD ≤2 Å (Bagheri *et al*., 2020; Elhady *et al*., 2021; Ferrari and Patrizio, 2021; Zhang *et al*., 2021; Zheng *et al*., 2022).

Table 1. The amino acid sequence of IDH1 (R132H) epitopes as a candidate glioma vaccine

| Epitope | Amino acid sequence | Epitope | Amino acid sequence | Epitope | Amino acid sequence |
|---|---|---|---|---|---|
| 1 | QYRATDFVVPGPGKV | 32 | LAFFANALEEVSIET | 63 | LVCPDGKTVEAEAAHGTVTR |
| 2 | YRATDFVVPGPGKVE | 33 | DLAACIKGLPNVQRS | 64 | VCPDGKTVEAEAAHGTVTRH |
| 3 | LVHNFEEGGGVAMGM | 34 | LAACIKGLPNVQRSD | 65 | CPDGKTVEAEAAHGTVTRHY |
| 4 | HNFEEGGGVAMGMYN | 35 | AACIKGLPNVQRSDY | 66 | PDGKTVEAEAAHGTVTRHYR |
| 5 | SIEDFAHSSFQMALS | 36 | ACIKGLPNVQRSDYL | 67 | YQKGQETSTNPIASIFAWTR |
| 6 | SSFQMALSKGWPLYL | 37 | TFEFMDKLGENLKIK | 68 | QKGQETSTNPIASIFAWTRG |
| 7 | SFQMALSKGWPLYLS | 38 | FEFMDKLGENLKIKL | 69 | KGQETSTNPIASIFAWTRGL |
| 8 | MALSKGWPLYLSTKN | 39 | KLGENLKIKLAQAKL | 70 | QETSTNPIASIFAWTRGLAH |
| 9 | LSKGWPLYLSTKNTI | 40 | SKKISGGSVVEMQGDEMTRI | 71 | ETSTNPIASIFAWTRGLAHR |
| 10 | KGWPLYLSTKNTILK | 41 | KKISGGSVVEMQGDEMTRII | 72 | TSTNPIASIFAWTRGLAHRA |
| 11 | GWPLYLSTKNTILKK | 42 | QKVTYLVHNFEEGGVAMGM | 73 | STNPIASIFAWTRGLAHRAK |
| 12 | WPLYLSTKNTILKKY | 43 | KVTYLVHNFEEGGVAMGMY | 74 | TNPIASIFAWTRGLAHRAKL |
| 13 | PLYLSTKNTILKKYD | 44 | TYLVHNFEEGGGVAMGMYNQ | 75 | PIASIFAWTRGLAHRAKLDN |

Table 1 continued.

| | | | | | |
|---|---|---|---|---|---|
| 14 | LYLSTKNTIL KKYDG | 45 | VTYLVHNFEEGGG VAMGMYN | 76 | IFAWTRGLAHRAK LDNNKEL |
| 15 | YLSTKNTILK KYDGR | 46 | SIEDFAHSSFQMAL SKGWPL | 77 | FAWTRGLAHRAKL DNNKELA |
| 16 | HRLIDDMVA QAMKSE | 47 | FAHSSFQMALSKG WPLYLST | 78 | AWTRGLAHRAKLD NNKELAF |
| 17 | RLIDDMVAQ AMKSEG | 48 | AHSSFQMALSKGW PLYLSTK | 79 | WTRGLAHRAKLDN NKELAFF |
| 18 | LIDDMVAQA MKSEGG | 49 | HSSFQMALSKGWP LYLSTKN | 80 | RAKLDNNKELAFF ANALEEV |
| 19 | PDGKTVEAE AAHGTV | 50 | SSFQMALSKGWPL YLSTKNT | 81 | AKLDNNKELAFFA NALEEVS |
| 20 | DGKTVEAEA AHGTVT | 51 | SFQMALSKGWPLY LSTKNTI | 82 | KLDNNKELAFFAN ALEEVSI |
| 21 | GKTVEAEAA HGTVTR | 52 | QMALSKGWPLYLS TKNTILK | 83 | LDNNKELAFFANA LEEVSIE |
| 22 | KTVEAEAAH GTVTRH | 53 | MALSKGWPLYLST KNTILKK | 84 | DNNKELAFFANAL EEVSIET |
| 23 | ASIFAWTRG LAHRAK | 54 | LSKGWPLYLSTKN TILKKYD | 85 | FMTKDLAACIKGLP NVQRSD |
| 24 | SIFAWTRGL AHRAKL | 55 | SKGWPLYLSTKNTI LKKYDG | 86 | MTKDLAACIKGLP NVQRSDY |
| 25 | FAWTRGLAH RAKLDN | 56 | KGWPLYLSTKNTIL KKYDGR | 87 | TKDLAACIKGLPNV QRSDYL |
| 26 | LDNNKELAF FANALE | 57 | GWPLYLSTKNTILK KYDGRF | 88 | SDYLNTFEFMDKL GENLKIK |
| 27 | DNNKELAFF ANALEE | 58 | WPLYLSTKNTILKK YDGRFK | 89 | DYLNTFEFMDKLG ENLKIKL |
| 28 | NNKELAFFA NALEEV | 59 | PLYLSTKNTILKKY DGRFKD | 90 | YLNTFEFMDKLGE NLKIKLA |
| 29 | NKELAFFAN ALEEVS | 60 | LYLSTKNTILKKYD GRFKDI | 91 | FEFMDKLGENLKIK LAQAKL |
| 30 | KELAFFANA LEEVSI | 61 | YLSTKNTILKKYDG RFKDIF | | |
| 31 | ELAFFANAL EEVSIE | 62 | VLVCPDGKTVEAE AAHGTVT | | |

During the docking process, epitope and receptors were prepared by adding hydrogen and charge, followed by generating surface of receptors using Chimera version 1.10.2 (Huang *et al*., 2014). The spherical form of the samples was then formed to obtain several clusters. Subsequently, one cluster of the receptors with the greatest number of spheres and native ligands was selected for further experimentation. A box was then created around the active side of the receptor, with an extra margin of 20 Å to be used for making the grid, and the process was continued with redocking. The redocking grid was also used for docking epitope to the receptors. The grid score was then obtained from the docking results, where a negative value indicated the presence of a greater affinity for epitope-receptor bond. The results were visualized using Discovery Studio (Jejurikar and Rohane, 2021), and epitope with the most negative grid score was selected for molecular dynamics simulation.

### 2.2 *Molecular Dynamics Simulations*

Molecular dynamics simulations were performed using GROMACS version 5.0.6 (Abraham *et al*., 2015, 2023), with a temperature of 300 K for epitope-MHC II and epitope-EphA3 complexes, which were selected in the previous stage. Furthermore, the simulation was performed for 25 ns and the LINear Constraint Solver (LINCS) algorithm was used in the AMBER99SB-ILDN force field. The structural changes observed were then analyzed based on the value of the RMSD. Visualization of the molecular dynamics simulations could be carried out using Visual Molecular Dynamics (VMD) version 1.9.2 (Mackoy *et al*., 2021; Spivak *et al*., 2023).

## 3. Results and Discussion

### *3.1 Docking Studies*

Redocking between receptors with native ligands in the Protein Data Bank (Figure 1) was performed first to validate the docking method. The native ligands of MHC II and EphA3 were peptide A2 and compound 164, respectively.

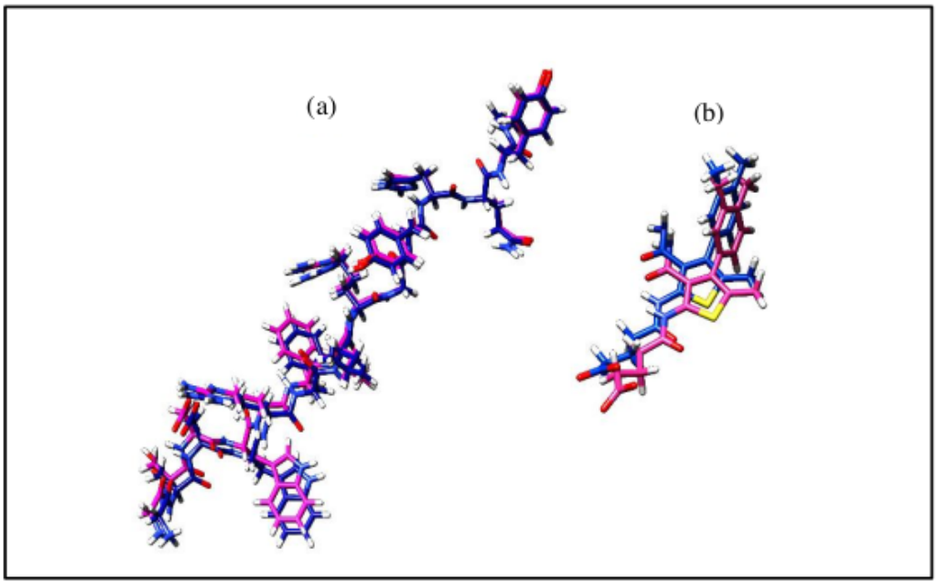


Figure 1. Comparison before (blue) and after (pink) redocking receptors with native ligands: native ligands MHC II, peptide A2 (a), and native ligands EphA3, compound 164 (b)

Furthermore, the results of redocking comprised RMSD value for MHC II with the A2 peptide (0.7371 Å) as well as receptor EphA3 with compound 164

(1.2801 Å). When the RMSD value was less than 2 Å, the algorithms and utilized parameters were adequate for determining the optimal docking pose. Therefore, the results obtained from the directed docking protocol are considered valid, ensuring the biological relevance of the docking poses and their corresponding energies (Elhady *et al*., 2021). RMSD values obtained from the process were < 2 Å, indicating that the method could be used for virtual screening using epitope.

The docking study used a 3D structure of 91 epitopes to determine their activity concerning receptors. The rigid body docking method was used, where the conformation of epitope/ligand and receptor were fixed despite the two molecules' altered spatial position and orientation. The rigid body docking is appropriate for complex systems with a high molecular weight, such as peptide-protein complexes. It is a simple technique because it requires a few calculations. The rigid body docking approach produces adequate or even better models for more complexes than flexible docking methods. However, flexible docking methods may achieve higher accuracy for some targets (Chen *et al*., 2020; Desta *et al*., 2020; Tao *et al*., 2020).

Epitope activity for glioma prevention and treatment was determined based on docking results for MHC II (Table 2) and EphA3 receptor (Table 3). Furthermore, the grid score was obtained from the results. The more negative the grid score, the stronger the interaction between epitope and the receptor. The grid score quantifies the intermolecular interactions between a protein and a ligand. The grid score is the total energy in the gas phase, including the van der Waals energy ($E_{vdW}$) and electrostatic energy ($E_{ele}$). $E_{vdW}$ is computed with a protein model that accounts for all its atoms using the Lennard-Jones 6-6 potential (6-9 potential). The calculation of $E_{ele}$ was performed using Coulomb's law, considering a distance-dependent dielectric, ε (r) = 4r (Prentis *et al*., 2022; Abdjan *et al*., 2023; Balius *et al*., 2024).

The results of docking with MHC II obtained the most negative grid score of -62.73 kcal/mol with seven hydrogen bonds from epitope 42 (Figure 2a). Although the grid score was less negative than the grid score obtained for redocking the A2 peptide to MHC II, epitope 42 remained likely to be a new candidate prophylactic vaccines for glioma. This was because the A2 peptide was an endogenous sample used in this study only to find the active side of MHC II (Murthy and Stern, 1997; Mamedov *et al*., 2020; Wang *et al*., 2022). Meanwhile, the results of docking with the EphA3 receptor showed the most negative grid score of -55.56 kcal/mol with 11 hydrogen bonds on epitope 54 (Figure 2b). This value was more negative compared with the score obtained for redocking compound 164 to the EphA3 receptor.

Table 2. Results of epitopes docking with MHC II

| Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) |
|---|---|---|---|---|---|---|---|---|---|
| A2 | -78.66 | 19 | -52.31 | 38 | -41.24 | 57 | -42.50 | 76 | -41.27 |
| 1 | -46.39 | 20 | -58.93 | 39 | -34.08 | 58 | -42.66 | 77 | -41.82 |
| 2 | -50.78 | 21 | -47.42 | 40 | -50.96 | 59 | -45.67 | 78 | -50.89 |
| 3 | -31.23 | 22 | -46.53 | 41 | -48.02 | 60 | -38.68 | 79 | -44.74 |
| 4 | -56.99 | 23 | -41.87 | 42 | -62.73 | 61 | -32.67 | 80 | -39.15 |
| 5 | -43.57 | 24 | -40.02 | 43 | -54.16 | 62 | -44.02 | 81 | -42.17 |
| 6 | -45.07 | 25 | -38.76 | 44 | -49.98 | 63 | -55.83 | 82 | -40.88 |
| 7 | -48.32 | 26 | -32.41 | 45 | -42.00 | 64 | -52.28 | 83 | -41.64 |
| 8 | -37.62 | 27 | -39.94 | 46 | -41.66 | 65 | -48.70 | 84 | -42.17 |
| 9 | -42.46 | 28 | -47.70 | 47 | -34.89 | 66 | -52.29 | 85 | -43.92 |
| 10 | -48.87 | 29 | -45.17 | 48 | -16.91 | 67 | -42.51 | 86 | -43.43 |
| 11 | -45.87 | 30 | -42.05 | 49 | -46.91 | 68 | -41.66 | 87 | -37.24 |
| 12 | -41.79 | 31 | -40.56 | 50 | -42.32 | 69 | -42.91 | 88 | -37.73 |
| 13 | -42.46 | 32 | -40.64 | 51 | -39.20 | 70 | -41.26 | 89 | -51.31 |
| 14 | -39.12 | 33 | -49.24 | 52 | -38.96 | 71 | -45.32 | 90 | -38.54 |
| 15 | -40.34 | 34 | -47.13 | 53 | -44.49 | 72 | -42.15 | 91 | -35.49 |
| 16 | -50.80 | 35 | -43.49 | 54 | -41.60 | 73 | -48.86 | | |
| 17 | -43.56 | 36 | -44.73 | 55 | -44.52 | 74 | -49.06 | | |
| 18 | -37.73 | 37 | -35.75 | 56 | -40.95 | 75 | -42.32 | | |

Table 3. Results of epitopes docking with EphA3 receptor

| Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) | Epitope | Grid score (kcal/mol) |
|---|---|---|---|---|---|---|---|---|---|
| 164 | -43.10 | 19 | -46.63 | 38 | -43.85 | 57 | -52.83 | 76 | -34.15 |
| 1 | -54.11 | 20 | -46.06 | 39 | -31.12 | 58 | -47.88 | 77 | -39.59 |
| 2 | -50.70 | 21 | -47.97 | 40 | -42.89 | 59 | -33.48 | 78 | -36.57 |
| 3 | -33.67 | 22 | -48.24 | 41 | -6.95 | 60 | -37.44 | 79 | -48.04 |
| 4 | -42.39 | 23 | -43.46 | 42 | -42.88 | 61 | -38.44 | 80 | -36.29 |
| 5 | -43.60 | 24 | -47.67 | 43 | -50.49 | 62 | -43.70 | 81 | -39.78 |
| 6 | -41.99 | 25 | -42.74 | 44 | -38.64 | 63 | -41.95 | 82 | -45.47 |
| 7 | -45.66 | 26 | -41.21 | 45 | -31.13 | 64 | -42.06 | 83 | -46.73 |
| 8 | -28.32 | 27 | -40.52 | 46 | -50.26 | 65 | -50.95 | 84 | -43.64 |
| 9 | -50.01 | 28 | -47.65 | 47 | -26.08 | 66 | -32.76 | 85 | -43.49 |
| 10 | -47.53 | 29 | -43.60 | 48 | -4.60 | 67 | -34.22 | 86 | -46.97 |
| 11 | -49.10 | 30 | -55.52 | 49 | -29.95 | 68 | -30.15 | 87 | -33.65 |
| 12 | -54.63 | 31 | -47.36 | 50 | -37.56 | 69 | -44.47 | 88 | -44.85 |
| 13 | -49.05 | 32 | -42.79 | 51 | -36.96 | 70 | -32.71 | 89 | -45.65 |
| 14 | -54.03 | 33 | -44.77 | 52 | -35.13 | 71 | -39.76 | 90 | -28.76 |
| 15 | -51.37 | 34 | -48.99 | 53 | -40.50 | 72 | -45.31 | 91 | -36.68 |
| 16 | -44.43 | 35 | -44.22 | 54 | -55.56 | 73 | -40.34 | | |
| 17 | -45.19 | 36 | -42.68 | 55 | -50.24 | 74 | -42.23 | | |
| 18 | -34.87 | 37 | -40.97 | 56 | -49.05 | 75 | -35.82 | | |

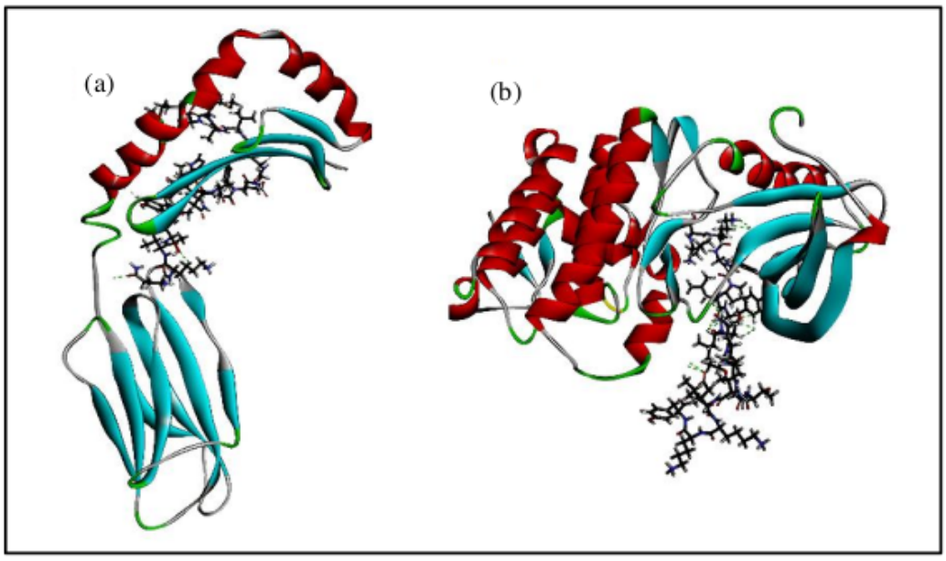


Figure 2. Visualization of docking results: epitope 42 to MHC II (a) and epitope 54 to the EphA3 receptor (b)

*3.2 Molecular Dynamics Simulations*

The molecular dynamics simulations were performed on epitope 42-MHC II and epitope 54-EphA3 receptor complexes. During the process, observation showed that epitope and receptors were flexible (Guterres and Im, 2020; Hashemzadeh *et al*., 2020; Lazim *et al*., 2020; Rampogu *et al*., 2022; Salo-Ahen *et al*., 2021). Furthermore, the simulations were carried out for 25 ns to determine the stability of docked epitope-receptor complexes.

The stability of epitope-receptor complex could be analyzed from changes in protein structural conformation during the simulation, as indicated by RMSD function and time. Energies and binding interactions between the ligand and protein influence the RMSD value. A protein structure is deemed stable and equilibrated when the RMSD < 3 Å (Santha and Vishwanathan, 2022). The simulation of epitope 42-MHC II led to a rapid increase in RMSD at the early stages, namely 17 Å at 1.67 ns. However, after 1.72-12.34 ns, the value decreased to about 4-8 Å. Although there was a major reduction, RMSD > 3 Å showed that the protein was unstable during the process because there were extensive conformational changes (Figure 3). Figure 4 shows the conformation changes of epitope 42-MHC II complex during the simulation.

During the molecular dynamics simulation of epitope 54-EphA3 receptor complex, RMSD fluctuations were stable from the beginning of the process up to 15.29 ns. Subsequently, the value increased drastically to 17 Å and

remained stable at 15.48 ns. The results showed that RMSD of epitope 54-EphA3 receptor complex was stable at 1.7-3.4 Å, as shown in Figure 5. At 15 ns in the simulation, the 3D form of epitope 54 changed from a coil to a β-sheet on the last seven amino acids, namely Asn, Thr, Ile, Leu, Lys, Tyr, and Asp (Figure 6).

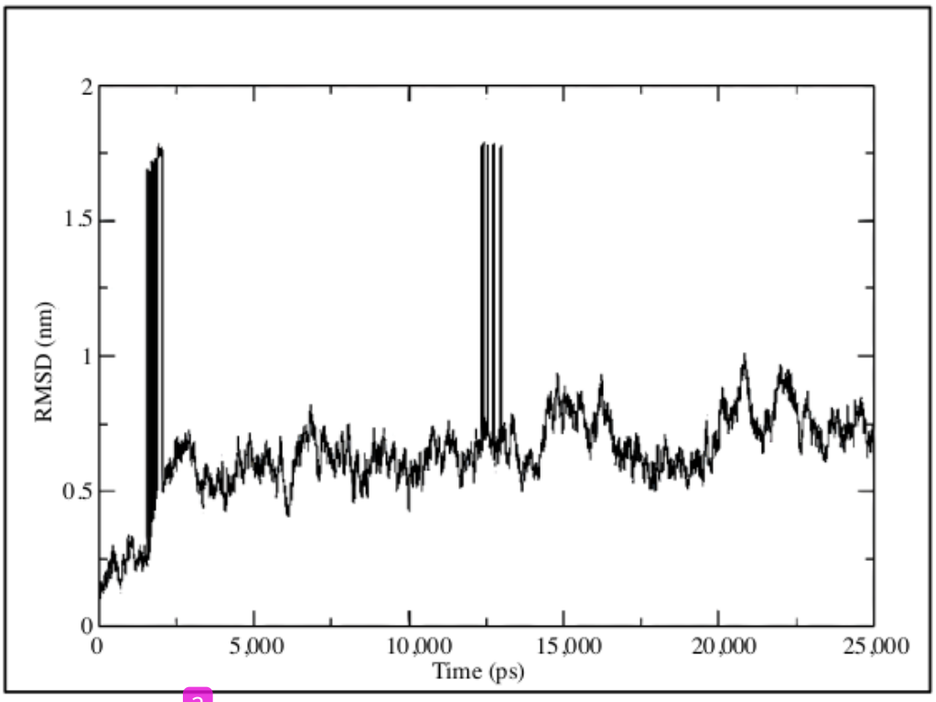


Figure 3. Chart of RMSD changes over time during molecular dynamics simulation of epitope 42-MHC II complex

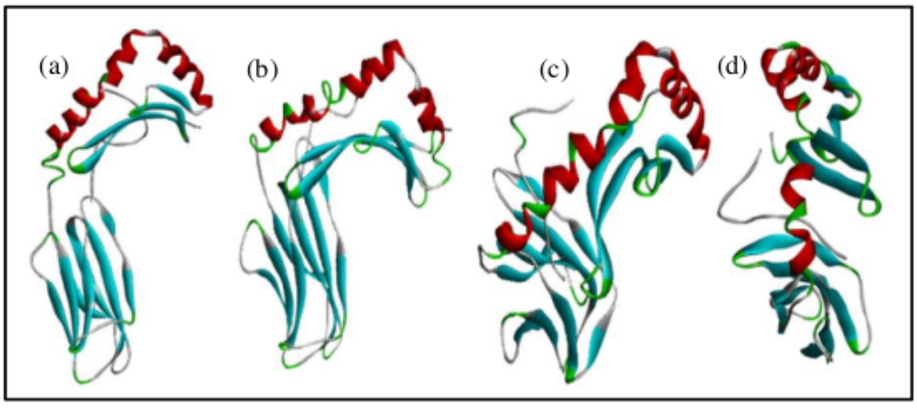


Figure 4. Conformation changes of epitope 42-MHC II complex during molecular dynamics simulation: time 0 ns (a), time 10 ns (b), time 15 ns (c), and time 25 ns (d)

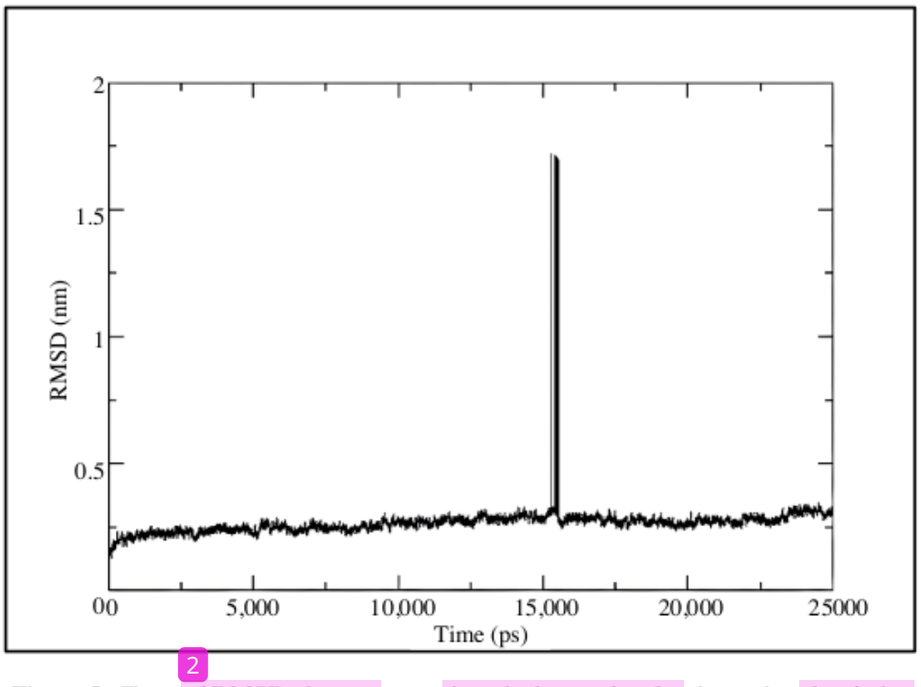


Figure 5. Chart of RMSD changes over time during molecular dynamics simulation of epitope 54-EphA3 receptor complex

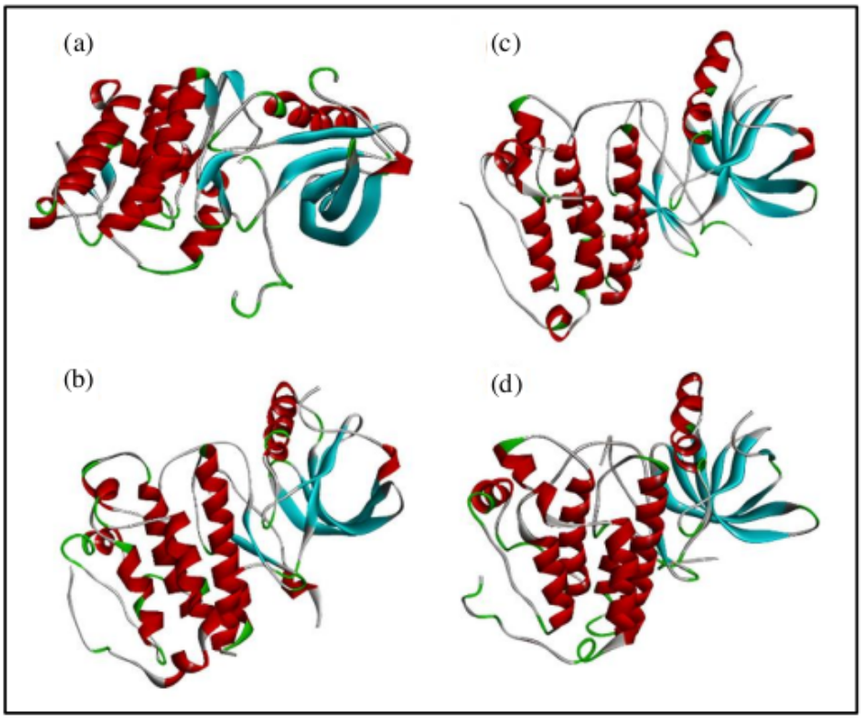


Figure 6. Conformation changes of epitope 54-EphA3 receptor complex during molecular dynamics simulation: time 0 ns (a), time 10 ns (b), time 15 ns (c), and time 25 ns (d)

The movement of atoms in the molecular dynamics simulation of complexes could be analyzed based on the RMSF values obtained during the process (Figure 7). The RMSF value was used to express the average quadratic fluctuation of the minimum distances between proteins and ligands seen in molecular dynamics simulations. The RMSF quantifies the degree of movement exhibited by each residue throughout a simulation, hence measuring individual residue flexibility. The RMSF of each system member provides information on the movement and stability of each residue in the simulation track. The RMSF graphic illustrates the fluctuation ratio at the residue level, indicating the amino acids in a protein that contribute the most to molecular motion (Sargolzaei, 2021; Meena *et al*., 2022; da Fonseca *et al*., 2023). Based on the results, the number of epitope atoms that fluctuated was higher compared with receptors. Atoms of epitope 42 and 54 began from the 3,013$^{th}$ and 4,450$^{th}$ atomic orders of the complex, respectively.

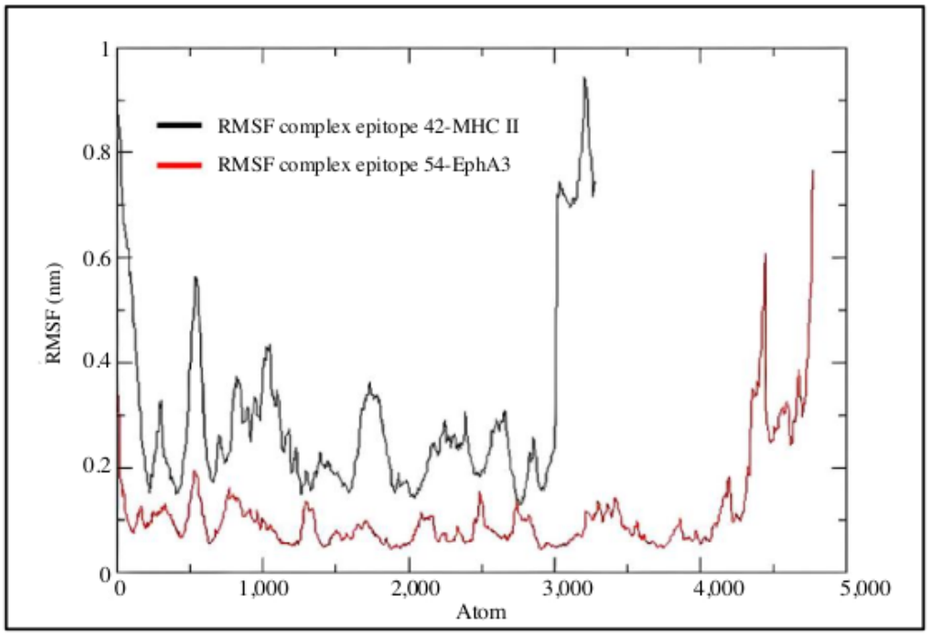


Figure 7. The RMSF chart of molecular dynamics simulations of epitope 42-MHC II complex and epitope 54-EphA3 receptor complex for 25 ns

## 4. Conclusion and Recommendation

The best glioma prophylactic and therapeutic vaccines among the 91 epitopes of IDH1 (R132H) were samples 42 and 54, respectively. The grid score of

epitope 42 docking into MHC II was -62.73 kcal/mol, while a value of -55.56 kcal/mol was obtained for docking epitope 54 into the EphA3 receptor. During molecular dynamics simulation with a temperature of 300 K, epitope 42-MHC II complex was unstable throughout the process. Meanwhile, the results showed that epitope 54-EphA3 complex was stable from the beginning of the process up to 15.29 ns. Based on these findings, it is important to synthesize epitope 42 and 54 as well as carry out further experimental testing in vitro with the Hs 683 cell line and in vivo to confirm their preventive and curative activity against glioma.

## 5. References

Abd-Aziz, N., & Poh, C.L. (2022). Development of peptide-based vaccines for cancer. Journal of Oncology, 2022, 1-17. https://doi.org/10.1155/2022/9749363

Abdjan, M.I., Aminah, N.S., Kristanti, A.N., Siswanto, I., Ilham, B., Wardana, A.P., & Takaya, Y. (2023). Structure-based approach: Molecular insight of pyranocumarins against α-glucosidase through computational studies. RSC Advances, 13(6), 3438-3447. https://doi.org/10.1039/d2ra07537g

Abraham, M., Alekseenko, A., Bergh, C., Blau, C., Briand, E., Doijade, M., Fleischmann, S., Gapsys, V., Garg, G., Gorelov, S., Gouaillardet, G., Gray, A., Irrgang, M. E., Jalalypour, F., Jordan, J., Junghans, C., Kanduri, P., Keller, S., Kutzner, C., … Lindahl, E. (2023). GROMACS 2023.3 manual. Retrieved from https://zenodo.org/records/10017699

Abraham, M., Hess, B., Spoel, D., & Lindahl, E. (2015). GROMACS user manual version 5.0.6. Retrieved from https://ftp.gromacs.org/pub/manual/manual-5.0.6.pdf

Ahsan, S.S. (2022). Association of isocitrate dehydrogenase1 mutation with various tumor types in brain tumor patients. Revista de Psiquiatria Clinica, 49(2), 11-24. https://doi.org/10.15761/0101-60830000000401

Arita, H., Narita, Y., Yoshida, A., Hashimoto, N., Yoshimine, T., & Ichimura, K. (2015). IDH1/2 mutation detection in gliomas. Brain Tumor Pathology, 32(2), 79-89. https://doi.org/10.1007/s10014-014-0197-x

Arora, S., Scott, A. M., & Janes, P.W. (2023). Eph Receptors in cancer. Biomedicines, 11(2), 315. https://doi.org/10.3390/biomedicines11020315

Bagheri, S., Behnejad, H., Firouzi, R., & Karimi-Jafari, M. H. (2020). Using the semiempirical quantum mechanics in improving the molecular docking: A case study with CDK2. Molecular Informatics, 39(9), 2000036. https://doi.org/10.1002/minf.202000036

Balius, T.E., Tan, Y.S., & Chakrabarti, M. (2024). DOCK 6: Incorporating hierarchical traversal through precomputed ligand conformations to enable large-scale docking. Journal of Computational Chemistry, 45(1), 47-63. https://doi.org/10.1002/jcc.27218

Baumgartner, U., D'Souza, R.C.J, Offenhauser, C., Akgul, S., & Day, B.W. (2021). Future perspectives: A review of therapeutic advances in recurrent glioblastoma. Journal of Cancer Science and Clinical Therapeutics, 5(2), 286-308. https://doi.org/10.26502/jcsct.5079118

Bunse, L., Bunse, T., Krämer, C., Chih, Y.C., & Platten, M. (2022). Clinical and translational advances in glioma immunotherapy. Neurotherapeutics, 19(6), 1799-1817. https://doi.org/10.1007/s13311-022-01313-9

Burley, S.K., Berman, H.M., Duarte, J.M., Feng, Z., Flatt, J.W., Hudson, B.P., Lowe, R., Peisach, E., Piehl, D.W., Rose, Y., Sali, A., Sekharan, M., Shao, C., Vallat, B., Voigt, M., Westbrook, J.D., Young, J.Y., & Zardecki, C. (2022). Protein data bank: A Comprehensive review of 3D structure holdings and worldwide utilization by researchers, educators, and students. Biomolecules, 12(10), 1425. https://doi.org/10.3390/biom12101425

Chen, G., Seukep, A.J., & Guo, M. (2020). Recent advances in molecular docking for the research and discovery of potential marine drugs. Marine Drugs, 18(11), 545. https://doi.org/10.3390/md18110545

Choi, D.J., Armstrong, G., Lozzi, B., Vijayaraghavan, P., Plon, S.E., Wong, T.C., Boerwinkle, E., Muzny, D.M., Chen, H.C., Gibbs, R.A., Ostrom, Q.T., Melin, B., Deneen, B., Bondy, M.L., Bainbridge, M.N., Amos, C.I., Barnholtz-Sloan, J.S., Bernstein, J.L., Claus, E.B., … Zarowiecki, M. (2023). The genomic landscape of familial glioma. Science Advances, 9(17), eade2675. https://doi.org/10.1126/SCIADV.ADE2675

Colopi, A., Fuda, S., Santi, S., Onorato, A., Cesarini, V., Salvati, M., Balistrieri, C.R., Dolci, S., & Guida, E. (2023). Impact of age and gender on glioblastoma onset, progression, and management. Mechanisms of Ageing and Development, 211, 111801. https://doi.org/10.1016/j.mad.2023.111801

da Fonseca, A.M., Caluaco, B.J., Madureira, J.M.C., Cabongo, S.Q., Gaieta, E.M., Djata, F., Colares, R.P., Neto, M. M., Fernandes, C.F.C., Marinho, G.S., dos Santos, H.S., & Marinho, E.S. (2023). Screening of potential inhibitors targeting the main protease structure of SARS-CoV-2 via molecular docking, and approach with molecular dynamics, RMSD, RMSF, H-Bond, SASA and MMGBSA. Molecular Biotechnology, 2023. https://doi.org/10.1007/s12033-023-00831-x

Delgado-Martín, B., & Medina, M.Á. (2020). Advances in the knowledge of the molecular biology of glioblastoma and its impact in patient diagnosis, stratification, and treatment. Advanced Science, 7(9), 1902971. https://doi.org/10.1002/advs.201902971

Desta, I.T., Porter, K.A., Xia, B., Kozakov, D., & Vajda, S. (2020). Performance and its limits in rigid body protein-protein docking. Structure, 28(9), 1071-1081. https://doi.org/10.1016/j.str.2020.06.006

Elhady, S.S., Abdelhameed, R.F.A., Malatani, R.T., Alahdal, A.M., Bogari, H.A., Almalki, A.J., Mohammad, K.A., Ahmed, S.A., Khedr, A.I.M., & Darwish, K.M. (2021). Molecular docking and dynamics simulation study of hyrtios erectus isolated scalarane sesterterpenes as potential sars-cov-2 dual target inhibitors. Biology, 10(5), 385. https://doi.org/10.3390/biology10050389

Ferrari, I.V., & Patrizio, P. (2021). Development and validation molecular docking analysis of human serum albumin (HSA). BioRxiv. https://doi.org/10.1101/2021.07.09.451789

Franceschi, E., De Biase, D., Di Nunno, V., Pession, A., Tosoni, A., Gatto, L., Tallini, G., Visani, M., Lodi, R., Bartolini, S., & Brandes, A.A. (2021). IDH1 non-canonical mutations and survival in patients with glioma. Diagnostics, 11(2), 342. https://doi.org/10.3390/diagnostics11020342

Fujita, Y., Nunez-Rubiano, L., Dono, A., Bellman, A., Shah, M., Rodriguez, J.C., Putluri, V., Kamal, A.H.M., Putluri, N., Riascos, R.F., Zhu, J.J., Esquenazi, Y., & Ballester, L.Y. (2022). IDH1 p.R132H ctDNA and D-2-hydroxyglutarate as CSF biomarkers in patients with *IDH*-mutant gliomas. Journal of Neuro-Oncology, 159(2), 261-270. https://doi.org/10.1007/s11060-022-04060-1

Guarra, F., & Colombo, G. (2023). Computational methods in immunology and vaccinology: Design and development of antibodies and immunogens. Journal of Chemical Theory and Computation, 19(16), 5315-5333. https://doi.org/10.1021/acs.jctc.3c00513

Guterres, H., & Im, W. (2020). Improving Protein-ligand docking results with high-throughput molecular dynamics simulations. Journal of Chemical Information and Modeling, 60(4), 2189-2198. https://doi.org/10.1021/acs.jcim.0c00057

Hasanzadeh, N., & Niknejad, A. (2021). Cerebral glioblastoma: A review on genetic alterations, signaling pathways, and clinical managements. Jentashapir Journal of Cellular and Molecular Biology, 12(4). https://doi.org/10.5812/jjcmb.119223

Hashemzadeh, H., Javadi, H., & Darvishi, M.H. (2020). Study of structural stability and formation mechanisms in DSPC and DPSM liposomes: A coarse-grained molecular dynamics simulation. Scientific Reports, 10(1), 1837. https://doi.org/10.1038/s41598-020-58730-z

Huang, C.C., Meng, E.C., Morris, J.H., Pettersen, E.F., & Ferrin, T.E. (2014). Enhancing UCSF Chimera through web services. Nucleic Acids Research, 42(W1), W478-W484. https://doi.org/10.1093/nar/gku377

Jejurikar, B.L., & Rohane, S.H. (2021). Drug designing in discovery studio. Asian Journal of Research in Chemistry, 14(2), 135-138. https://doi.org/10.5958/0974-4150.2021.00025.0

Kaczmarek, M., Poznańska, J., Fechner, F., Michalska, N., Paszkowska, S., Napierała, A., & Mackiewicz, A. (2023). Cancer vaccine therapeutics: Limitations and effectiveness – A literature review. Cells, 12(17), 2159. https://doi.org/10.3390/cells12172159

Kalita, P., & Tripathi, T. (2022). Methodological advances in the design of peptide-based vaccines. Drug Discovery Today, 27(5), 1367-1380. https://doi.org/10.1016/j.drudis.2022.03.004

Karpel-Massler, G., Nguyen, T.T.T., Shang, E., & Siegelin, M.D. (2019). Novel IDH1-targeted glioma therapies. CNS Drugs, 33, 1155-1166. https://doi.org/10.1007/s40263-019-00684-6

Ko, C., & Brody, J.P. (2021). A genetic risk score for glioblastoma multiforme based on copy number variations. Cancer Treatment and Research Communications, 27, 100352. https://doi.org/10.1016/j.ctarc.2021.100352

Lang, T.P., Moustakas, D., Brozell, S., Carrascal, N., Mukherjee, S., Balius, T., Allen, W.J., Holden, P., Pegg, S., Raha, K., Shivakumar, D., Rizzo, R., Case, D., Shoichet, B., & Kuntz, I. (2015). DOCK 6.7 user's manual. Retrieved from https://dock.compbio.ucsf.edu/DOCK_6/dock6_manual.htm

Lazim, R., Suh, D., & Choi, S. (2020). Advances in molecular dynamics simulations and enhanced sampling methods for the study of protein systems. International Journal of Molecular Sciences, 21(17), 6339. https://doi.org/10.3390/ijms21176339

Liu, D., Che, X., Wang, X., Ma, C., & Wu, G. (2023). Tumor vaccines: Unleashing the power of the immune system to fight cancer. Pharmaceuticals, 16(10), 1384. https://doi.org/10.3390/ph16101384

Mackoy, T., Kale, B., Papka, M.E., & Wheeler, R.A. (2021). viewSq, a Visual Molecular Dynamics (VMD) module for calculating, analyzing, and visualizing X-ray and neutron structure factors from atomistic simulations. Computer Physics Communications, 264, 107881. https://doi.org/10.1016/j.cpc.2021.107881

Mamedov, A., Vorobyeva, N., Filimonova, I., Zakharova, M., Kiselev, I., Bashinskaya, V., Baulina, N., Boyko, A., Favorov, A., Kulakova, O., Ziganshin, R., Smirnov, I., Poroshina, A., Shilovskiy, I., Khaitov, M., Sykulev, Y., Favorova, O., Vlassov, V., Gabibov, A., & Belogurov, A. (2020). Protective allele for multiple sclerosis HLA-DRB1*01:01 provides kinetic discrimination of myelin and exogenous antigenic peptides. Frontiers in Immunology, 10, 3088. https://doi.org/10.3389/fimmu.2019.03088

Matteo, D.A., Grunseth, A.J., Gonzalez, E.R., Anselmo, S.L., Kennedy, M.A., Moman, P., Scott, D.A., Hoang, A., & Sohl, C.D. (2017). Molecular mechanisms of isocitrate dehydrogenase 1 (IDH1) mutations identified in tumors: The role of size and hydrophobicity at residue 132 on catalytic efficiency. Journal of Biological Chemistry, 292(19), 7971-7983. https://doi.org/10.1074/jbc.M117.776179

Meena, M.K., Kumar, D., Kumari, K., Kaushik, N.K., Kumar, R.V., Bahadur, I., Vodwal, L., & Singh, P. (2022). Promising inhibitors of nsp2 of CHIKV using molecular docking and temperature-dependent molecular dynamics simulations. Journal of Biomolecular Structure and Dynamics, 40(13), 5827-5835. https://doi.org/10.1080/07391102.2021.1873863

Mirchia, K., & Richardson, T.E. (2020). Beyond IDH-mutation: Emerging molecular diagnostic and prognostic features in adult diffuse gliomas. Cancers 12(7), 1817. https://doi.org/10.3390/cancers12071817

Murthy, V.L., & Stern, L.J. (1997). The class II MHC protein HLA-DR1 in complex with an endogenous peptide: Implications for the structural basis of the specificity of peptide binding. Structure, 5(10), 1385-1396. https://doi.org/10.1016/S0969-2126(97)00288-8

Platten, M., Bunse, L., Wick, A., Bunse, T., Le Cornet, L., Harting, I., Sahm, F., Sanghvi, K., Tan, C.L., Poschke, I., Green, E., Justesen, S., Behrens, G.A., Breckwoldt, M.O., Freitag, A., Rother, L.M., Schmitt, A., Schnell, O., Hense, J., … Wick, W. (2021). A vaccine targeting mutant IDH1 in newly diagnosed glioma. Nature, 592(7854), 463-468. https://doi.org/10.1038/s41586-021-03363-z

Prentis, L.E., Singleton, C.D., Bickel, J.D., Allen, W.J., & Rizzo, R.C. (2022). A molecular evolution algorithm for ligand design in DOCK. Journal of Computational Chemistry, 43(29), 1942-1963. https://doi.org/10.1002/jcc.26993

Rampogu, S., Lee, G., Park, J.S., Lee, K.W., & Kim, M.O. (2022). Molecular docking and molecular dynamics simulations discover curcumin analogue as a plausible dual inhibitor for SARS-CoV-2. International Journal of Molecular Sciences, 23(3), 1771. https://doi.org/10.3390/ijms23031771

Rawal, K., Sinha, R., Abbasi, B.A., Chaudhary, A., Nath, S.K., Kumari, P., Preeti, P., Saraf, D., Singh, S., Mishra, K., Gupta, P., Mishra, A., Sharma, T., Gupta, S., Singh, P., Sood, S., Subramani, P., Dubey, A.K., Strych, U., … Bottazzi, M.E. (2021). Identification of vaccine targets in pathogens and design of a vaccine using computational approaches. Scientific Reports, 11(1), 17626. https://doi.org/10.1038/s41598-021-96863-x

Salo-Ahen, O.M.H., Alanko, I., Bhadane, R., Alexandre, A.M., Honorato, R.V., Hossain, S., Juffer, A.H., Kabedev, A., Lahtela-Kakkonen, M., Larsen, A.S., Lescrinier, E., Marimuthu, P., Mirza, M.U., Mustafa, G., Nunes-Alves, A., Pantsar, T., Saadabadi, A., Singaravelu, K., & Vanmeert, M. (2021). Molecular dynamics simulations in drug discovery and pharmaceutical development. Processes, 9(1), 71. https://doi.org/10.3390/pr9010071

Santha, S.S.R., & Vishwanathan, A.S. (2022). Mechanistic insights into 5-lipoxygenase inhibition by pyocyanin: A molecular docking and molecular dynamics study. Journal of Biomolecular Structure and Dynamics, 40(20), 9752-9760. https://doi.org/10.1080/07391102.2021.1934543

Sargolzaei, M. (2021). Effect of nelfinavir stereoisomers on coronavirus main protease: Molecular docking, molecular dynamics simulation and MM/GBSA study. Journal of Molecular Graphics and Modelling, 103, 107803. https://doi.org/10.1016/j.jmgm.2020.107803

Senhaji, N., Houssaini, A.S., Lamrabet, S., Louati, S., & Bennis, S. (2022). Molecular and circulating biomarkers in patients with glioblastoma. International Journal of Molecular Sciences, 23(13), 7474. https://doi.org/10.3390/ijms23137474

Shayanfar, N., Zare-Mirzaie, A., Mohammadpour, M., Jafari, E., Mehrtash, A., Emtiazi, N., & Tajik, F. (2023). Low expression of isocitrate dehydrogenase 1 (IDH1) R132H is associated with advanced pathological features in laryngeal squamous cell carcinoma. Journal of Cancer Research and Clinical Oncology, 149(8), 4253-4267. https://doi.org/10.1007/s00432-022-04336-z

Siebenmorgen, T., & Zacharias, M. (2020). Computational prediction of protein-protein binding affinities. Wiley Interdisciplinary Reviews: Computational Molecular Science, 10(3), e1448. https://doi.org/10.1002/wcms.1448

Soleymani, S., Tavassoli, A., & Housaindokht, M.R. (2022). An overview of progress from empirical to rational design in modern vaccine development, with an emphasis on computational tools and immunoinformatics approaches. Computers in Biology and Medicine, 140, 105057. https://doi.org/10.1016/j.compbiomed.2021.105057

Spivak, M., Stone, J.E., Ribeiro, J., Saam, J., Freddolino, P.L., Bernardi, R.C., & Tajkhorshid, E. (2023). VMD as a platform for interactive small molecule preparation and visualization in quantum and classical simulations. Journal of Chemical Information and Modeling, 63(15), 4664-4678. https://doi.org/10.1021/acs.jcim.3c00658

Sunita, Sajid, A., Singh, Y., & Shukla, P. (2020). Computational tools for modern vaccine development. Human Vaccines and Immunotherapeutics, 16(3), 723-735. https://doi.org/10.1080/21645515.2019.1670035

Supandi, Yeni, & Dwita, L.P. (2021). Docking studies and molecular dynamics simulation of compounds contained in *Kaempferia galanga* L. to lipoxygenase (LOX) for anti-inflammatory drugs. Journal of Mathematical and Fundamental Sciences, 53(2). https://doi.org/10.5614/j.math.fund.sci.2021.53.2.4

Tangella, A.V., Gajre, A., & Kantheti, V.V. (2023). Isocitrate dehydrogenase 1 mutation and ivosidenib in patients with acute myeloid leukemia: A comprehensive review. Cureus, 15(9). https://doi.org/10.7759/cureus.44802

Tao, X., Huang, Y., Wang, C., Chen, F., Yang, L., Ling, L., Che, Z., & Chen, X. (2020). Recent developments in molecular docking technology applied in food science: A review. International Journal of Food Science and Technology, 55(1), 33-45. https://doi.org/10.1111/ijfs.14325

Testa, U., Castelli, G., & Pelosi, E. (2020). Isocitrate dehydrogenase mutations in myelodysplastic syndromes and in acute myeloid leukemias. Cancers, 12(9), 2427. https://doi.org/10.3390/cancers12092427

Wang, J., Wu, Y., Chen, Z., Chen, Y., Lin, Q., & Liang, Y. (2022). Exogenous bioactive peptides have a potential therapeutic role in delaying aging in rodent models. International Journal of Molecular Sciences, 23(3), 1421. https://doi.org/10.3390/ijms23031421

Yeni, & Tjahjono, D.H. (2017). Homology modeling of isocitrate dehydrogenase type 1 (R132H) epitopes using MODELLER, I-TASSER and (PS)2 for glioma vaccine. Farmasains 4(1), 21-32. https://doi.org/10.22236/farmasains.v4i1.189

Yeni, Y., Rachmania, R.A., & Mochamad, D.Y.M.R. (2021). Affinity of compounds in *Hemigraphis alternata* (Burm.F.) T. Ander leaves to cyclooxygenase 1 (COX-1): In silico approach. Proceedings of the 4th International Conference on Sustainable Innovation 2020–Health Science and Nursing (ICoSIHSN 2020), Yogyakarta, Indonesia, 552-555.

Yeni, Y., Supandi, S., Dwita, L.P., Suswandari, S., Shaharun, M.S., & Sambudi, N.S. (2020). Docking studies and molecular dynamics simulation of ipomoea batatas L. leaves compounds as lipoxygenase (LOX) inhibitor. Journal of Pharmacy and Bioallied Sciences, 12(Suppl 2), S836. https://doi.org/10.4103/jpbs.JPBS_103_20

Yu, G., He, X., Li, X., & Wu, Y. (2022). Driving neoantigen-based cancer vaccines for personalized immunotherapy into clinic: A burdensome journey to promising land. Biomedicine and Pharmacotherapy, 153, 113464. https://doi.org/10.1016/j.biopha.2022.113464

Zhang, Xiangyu, Yan, J., Wang, H., Wang, Y., Wang, J., & Zhao, D. (2021). Molecular docking, 3D-QSAR, and molecular dynamics simulations of thieno[3,2-b]pyrrole derivatives against anticancer targets of KDM1A/LSD1. Journal of Biomolecular Structure and Dynamics, 39(4), 1189-1202. https://doi.org/10.1080/07391102.2020.1726819

Zhang, X., Cui, H., Zhang, W., Li, Z., & Gao, J. (2023). Engineered tumor cell-derived vaccines against cancer: The art of combating poison with poison. Bioactive Materials, 22, 491-517. https://doi.org/10.1016/j.bioactmat.2022.10.016

Zheng, J., Su, Z., Kong, Y., Lin, Q., Liu, H., Wang, Y., & Wang, J. (2020). LncRNAs predicted to interfere with the gene regulation activity of miR-637 and miR-196a-5p in GBM. Frontiers in Oncology, 10, 303. https://doi.org/10.3389/fonc.2020.00303

Zheng, L., Meng, J., Jiang, K., Lan, H., Wang, Z., Lin, M., Li, W., Guo, H., Wei, Y., & Mu, Y. (2022). Improving protein-ligand docking and screening accuracies by incorporating a scoring function correction term. Briefings in Bioinformatics, 23(3), bbac051. https://doi.org/10.1093/bib/bbac051

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16

PAGE 17

PAGE 18

PAGE 19

PAGE 20