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DISCOVERY OF TIGIT-TARGETED SMALL MOLECULES AS CANCER THERAPIES

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Abstract

This paper will discuss the results of experiments done on the immune checkpoint TIGIT and the discovery of potential immune checkpoint inhibitors that can bind to it. First, machine learning was used to find potential binding spots on TIGIT and the requirements it needs to bind. Next came the pharmacophore test, a list filled with drugs that are able to bind to TIGIT; 15 were chosen at random. Each drug was then tested using SwissDock, which will find the site that it will best bind with TIGIT. After that, the properties of each drug were analyzed; if it passed Lipinski's Rule, it would go on to the next experiment. Last is the toxicity test, where the toxicity level and traits of each drug were analyzed, and in the end, three drugs were chosen that had the best overall results. The study turned out to be successful, as in the end, 3 drugs were found that have the potential to act as immune checkpoint inhibitors. Although this study was successful, it is not the end of the experiment, as many more drugs can be tested with the same processes.

Keywords: *Translational Medical Sciences, Drug Identification and Testing, Immune Cell and Target, Immune Checkpoint, TIGIT*

Introduction

In this research, we explored one of the immunity checkpoints called TIGIT that serves as a biomarker for early detection of cancer cells. However, it also stops the body's immune system from attacking the cancer cells. The goal of this project is to develop an immune checkpoint inhibitor that can prevent the TIGIT immunity checkpoint from binding to the cancer cell and allow the body's immune system to target and attack the cancer cells before they spread. Currently, there are existing inhibitors for a few other checkpoints, which have been extremely useful, but none have yet been discovered for TIGIT.

In today's world, many people are affected by cancer, and it is one of the leading causes of death worldwide. Statistics have shown that around 1 in 4 people worldwide have cancer, and 1 in 10 will die of cancer (Roy & Saikia, 2016). This shows how much impact cancer has on the lives of people worldwide.

Chemotherapy and radiotherapy have been the main ways of treating cancer (Cao et all, 2013). Chemotherapy involves treatments where drugs contain chemicals that can kill fast-growing cells, such as cancer cells, in the body. Radiotherapy involves using beams of high doses that can slow the growth of cancer cells by damaging their DNA to stop them from dividing (Sridhar & Symonds, 2009; McEntee 1995).

There are many different types of immune checkpoints, all acting as biomarkers that can be used for early detection of cancer cells in the body (Topalian et all, 2016). However, as stated earlier, these checkpoints actually stop the body from attacking these cancer cells and allow them to grow into tumors. To prevent this from happening, a checkpoint would need the presence of an inhibitor to allow the body's immune system to attack the cancer cells (Gubser et all, 2022).

Immune checkpoint inhibitors are proteins that can bind to the immune checkpoints and prevent them from stopping the body's immune system from attacking the cancer cells (Li et all, n.d.). Since the discovery of inhibitors for other checkpoints, there has been a massive improvement in treatment for cancer (Jenkins et all, 2018). However, none has yet been discovered for TIGIT.

The procedure involving immune checkpoint inhibitors is immunotherapy. Ever since, immune checkpoint inhibitors have been a massive success in advancements in cancer treatments (Cai et all, 2023), immunotherapy has been a standard option in treatment (Zhang & Zhang, 2020; Farkona, 2016).

The immunity checkpoint that would be focused on in this experiment is TIGIT, also known as T-cell immunoreceptors. Like all immunity checkpoints, TIGIT prevents the body from attacking cancer cells (Ge et all, 2021). Currently, no inhibitors have been discovered for it yet. This makes the goal of this experiment to discover at least one protein that can act as an inhibitor for TIGIT (Chauvin & Zarour, 2020).

Methods

2.1. Analysis of binding sites in TIGIT

2.1.1. ProteinPlus

By using the code for TIGIT, 5v52, ProteinPlus was able to create a replica of TIGIT, which is used as a base model for the experiment. Then, by enabling DoGSiteScorer, which would find every possible binding spot, it gave me a list of pockets with information on their volume, surface area, and drug score. This information would help determine which protein can best bind with TIGIT in certain pockets.

2.1.2. FT site

After loading up the FT site, I input the code for TIGIT, 5v52, along with some other information like email and job name. Afterward, it will start generating the model. After a while, it would generate the model along with binding sites that rely on energy levels. Each different binding site is labeled with a different color, similar to ProteinPlus.

2.1.3. PrankWeb

After loading up PrankWeb, I input the code for TIGIT, 5v52. Previously, ProteinPlus used shape and size to determine binding sites, and the FT site uses energy level. PrankWeb determines sites based on both. After the model loads up, I changed the polymer coloring from only white to conservation, as it gives a slightly better visual model. On the right, it will show information on sites, pockets that the algorithm detects.

2.2 Potential Inhibitors test for TIGIT

2.2.1 Pharmacophore

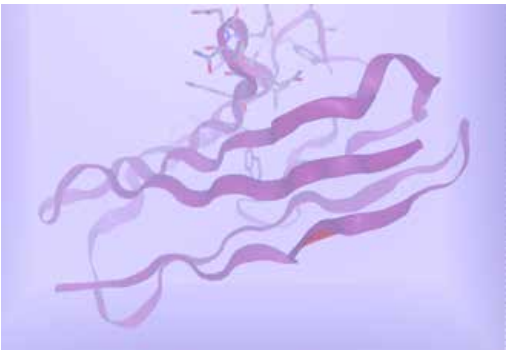
For the Pharmacophore model, I used the Pharmit website, and by entering the TIGIT code, 5v52, it generated a model of TIGIT. The Ligand and Receptors were then turned off, as the only thing needed visible were the Hydrogen Donors and Acceptors. (Figure 1) Then, by clicking "Search MolPort", it will search for every drug that can have the shape needed to connect to both the donor and acceptors, 15 of which will be used in the experiment.

Figure 1. *Picture of 2 Hydrogen Acceptors, orange, and 1 Hydrogen Donor, white. Ligands and Receptors also turned off*

2.2.2 Drug Test (SwissDock)

For the drug Test with SwissDock, I first ran each drug on the drug shop website to find its corresponding SMILES code, which was entered as the ligand. I then set TIGIT, using code 5v52, as the target and selected the chain to keep, T-cell immunoreceptor with Ig and ITIM domains for all tests, and no heteroatoms to keep. I then used the coordinates below for the area of the search box, making sure it covers the whole receptor. (Figure 2) After this, I checked the parameter, which would give an estimate of how long it would take, around a minute for every drug in this experiment. After everything was finished, the start docking button was hit, and the testing began.

Figure 2. *Image of box for Molport-019–897–498, coordinates are Center: –5, 6, –38; Box Size: 44, 25, 30. Same ones will be used for all other drugs*



2.2.3 Drug Test P. 2 (SwissADME)

First, I loaded up the SwissADME app, which requires the SMILES code for each drug being tested. The requirements that each drug has to pass are Lipinski's Rule, stating that each molecule can have no more than 5 hydrogen donors, 10 hydrogen acceptors, a mass of less than 500 daltons, and a calculated LogP of no more than 5. If it meets all the requirements, it can move on to the next experiment.

2.2.4 Toxicity Test

After loading the Pro-Tox website, I selected the toxicity prediction. For the toxicity test, I first got the SMILE code for each drug that passed Lipinski's Rule, all except for Molport-001–947–650. After loading the drug, all of the toxicity models are selected so that it can predict the toxicity of every effect the drug might have on the body.

Results and Discussion

3.1. Analysis of binding sites in TIGIT

3.1.1. ProteinPlus

After generating a list of possible pockets using DoGSiteScorer, there were 19 total, each corresponding to its own color, as shown in the generated result. (Figure 3) Each of the pockets has a volume of around 100A3–500A3, a surface area of around 200A2–700A2, and a drug score of less than one. (Table 1)

Figure 3. *Model result of predicted binding sites in TIGIT using the geometric method ProteinPlus. Colored spheres represent the binding sites*

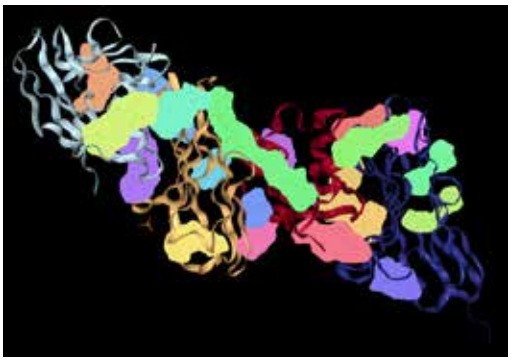


Table 1. *Summary of the predicted binding sites in TIGIT using Protein Plus*

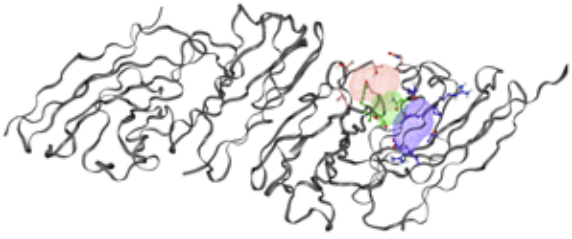
Name	Volume (A^3)	Surface Area (A^2)	Drug Score
P_0	508.4	721.95	0.72
P_1	457.47	641.42	0.69
P_2	417.89	581.35	0.8
P_3	363.44	642.32	0.65
P_4	299.83	552.72	0.62

Name	Volume (A^3)	Surface Area (A^2)	Drug Score
P_5	262.16	388.88	0.62
P_6	240.8	348.85	0.59
P_7	224.01	461.21	0.35
P_8	222.97	388.97	0.31
P_9	215.62	394.09	0.35
P_10	207.04	512.96	0.39
P_11	178.05	307.53	0.36
P_12	164.32	311.82	0.33
P_13	158.21	225.41	0.37
P_14	151.63	262.3	0.29
P_15	151.16	367.85	0.51
P_16	118.92	384.76	0.41
P_17	105.0	251.97	0.21
P_18	102.42	328.18	0.4

3.1.2. FT site

After running the test on the FT site, the result generated showed three different binding sites. This means that there are only three sites on TIGIT that rely on the energy level of the drugs to find, which is significantly less compared to the geometric shape shown earlier. The three sites' location is shown in the results. (Figure 4)

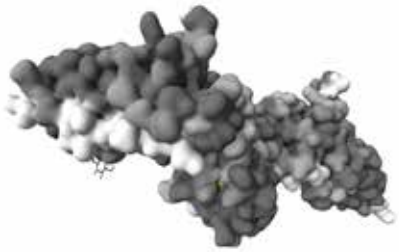
Figure 4. *Model result of potential binding sites generated from FT Sites, three binding sites found are shown in different colors*



3.1.3. PrankWeb

After generating the model (Figure 5), the algorithm suggests that no pockets were found, meaning all of the sites found previously in ProteinPlus and FT sites all relied on either energy level or specific shape, and none relied on both.

Figure 5. *Model result of potential binding sites generated from PrankWeb, no binding sites found as none relied on both shape and energy level*

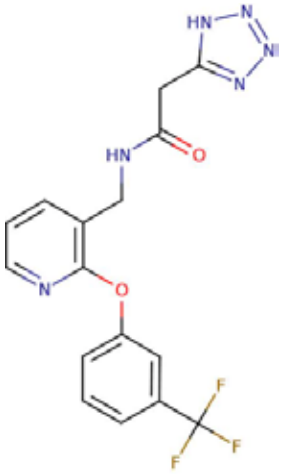
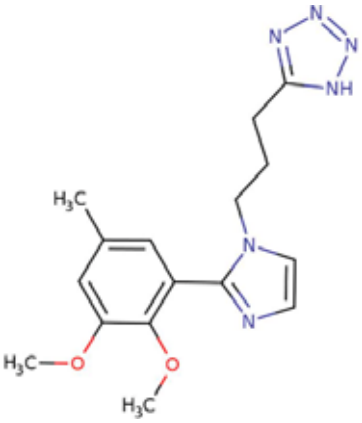
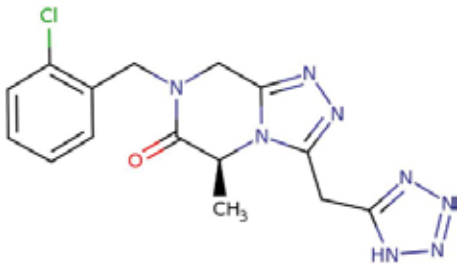
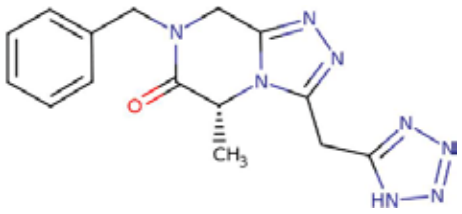
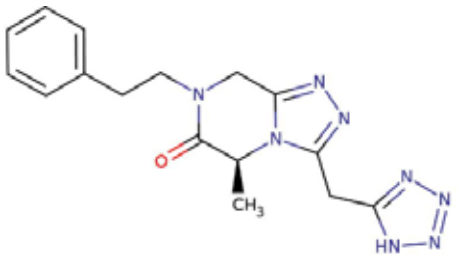


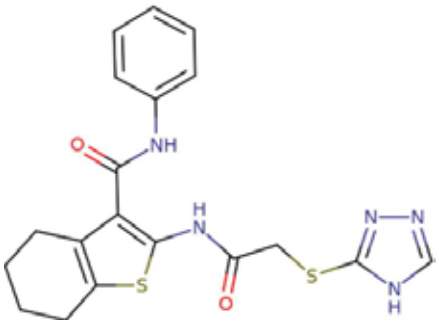
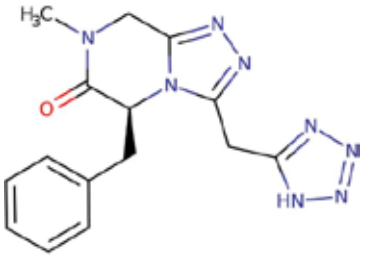
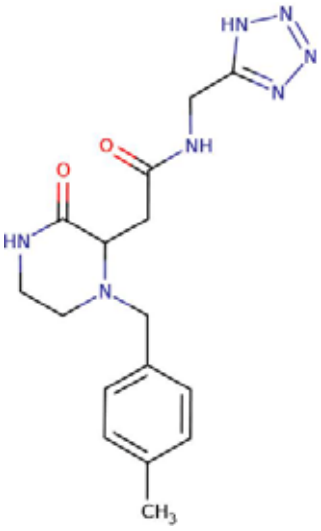
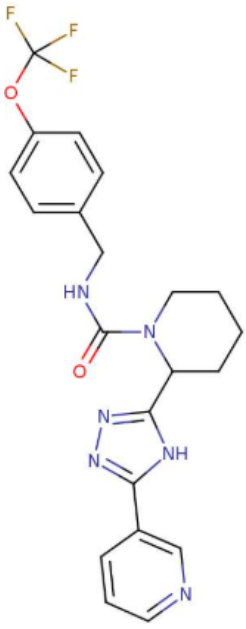
3.2 Analyzing Potential Inhibitors Test for TIGIT

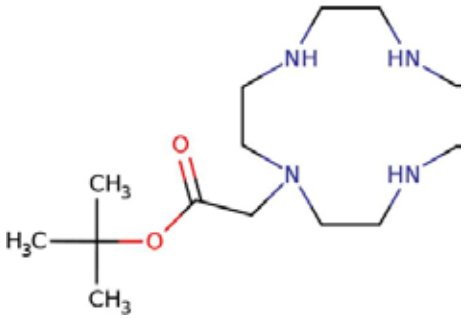
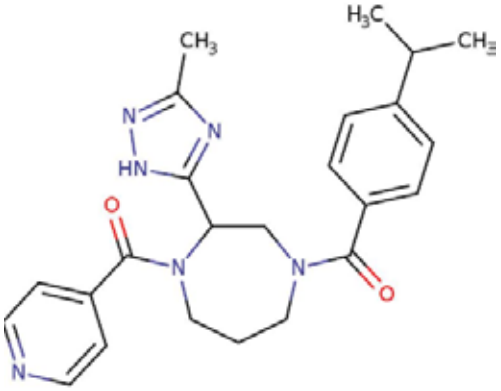
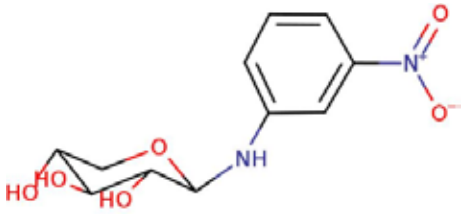
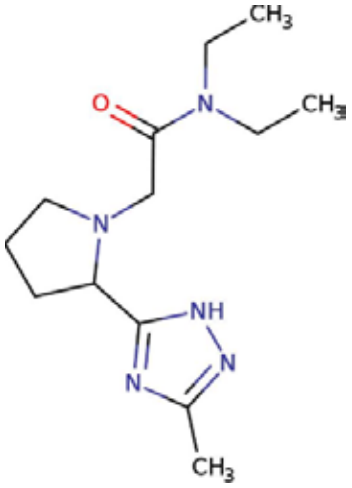
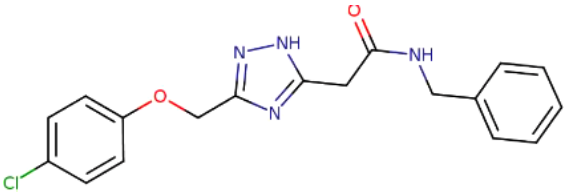
3.2.1 Pharmacophore

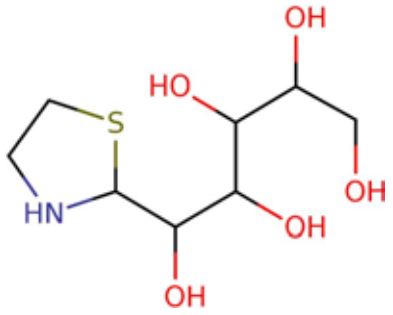
After deselecting the ligands and receptors, making sure two hydrogen acceptors and one donor are present, and searching for drugs, it generated a list with millions of different drugs that can fit the pattern of the acceptors and donors that were shown in Figure 1. In this experiment, 15 of these will be used for the Swiss testing phase. (Table 2) Each of these drugs also has a different RMSD, deviation score, which is how similar the computer simulation is compared to a real-life 3D model; the lower the score, the better.

Table 2. *Information on 15 selected drugs from Pharmacophore hydrogen donor + acceptor pattern*

Name	RMSD	Mass	RBnds	Picture
Mol-port-019–897–498	0.004	378	8	
Mol-port-051–532–927	0.005	328	7	
Mol-port-051–462–100	0.005	359	4	
Mol-port-051–454–708	0.005	324	4	
Mol-port-051–452–917	0.006	338	5	

Name	RMSD	Mass	RBnds	Picture
Mol-port-002–621–450	0.008	414	8	
Mol-port-051–470–239	0.009	324	4	
Mol-port-020–229–987	0.009	343	7	
Mol-port-044–334–503	0.009	446	8	

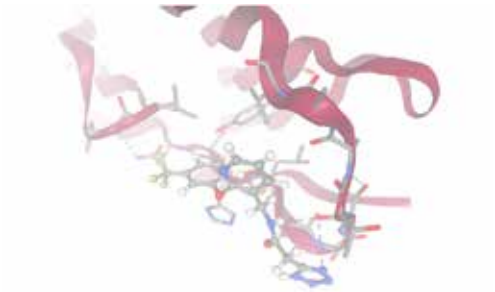
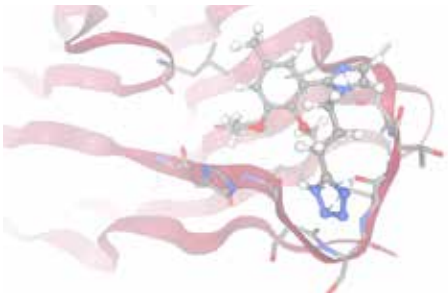
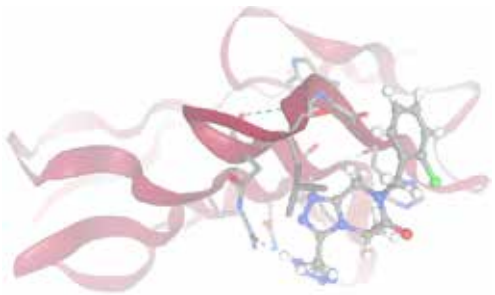
Name	RMSD	Mass	RBnds	Picture
Mol-port-051–517–110	0.009	286	4	
Mol-port-046–059–093	0.010	433	6	
Mol-port-000–814–864	0.010	270	3	
Mol-port-039–048–085	0.011	265	6	
Mol-port-005–953–974	0.011	357	8	

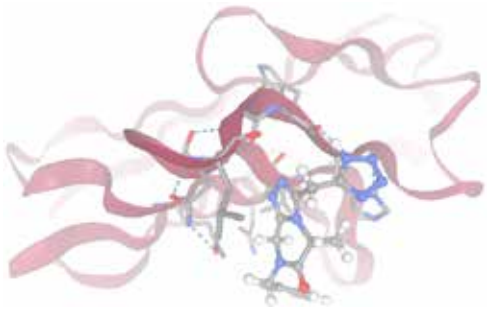
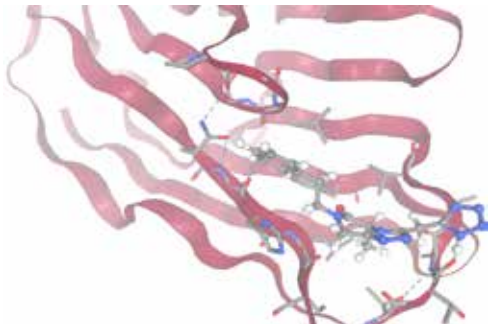
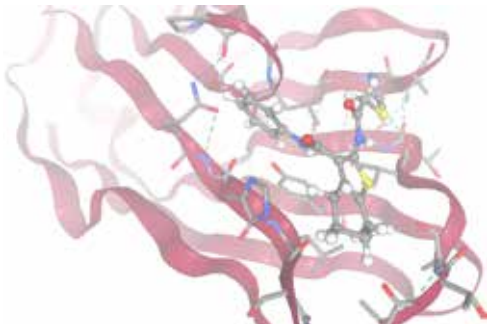
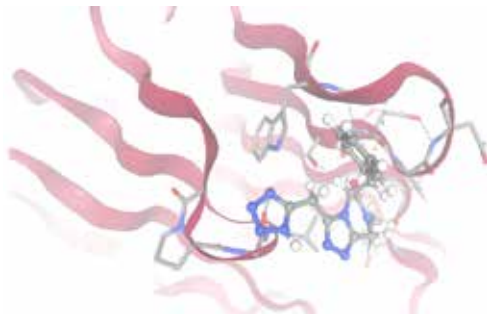
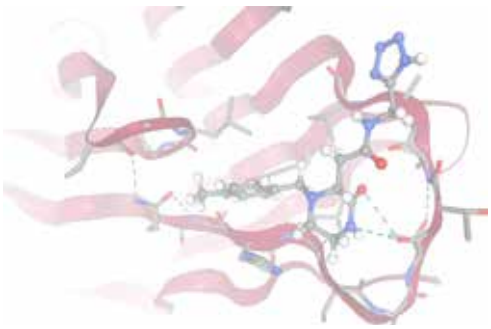
Name	RMSD	Mass	RBnds	Picture
Mol-port-001–947–650	0.011	239	5	

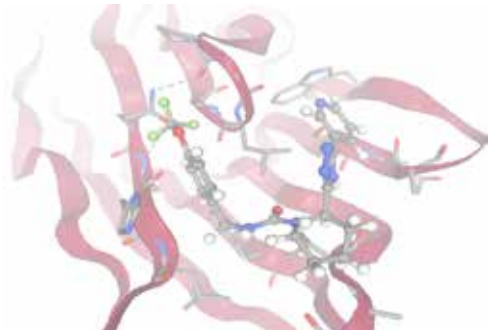
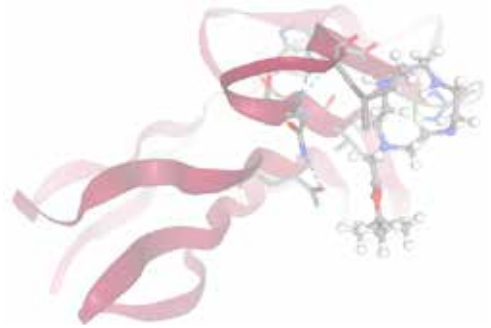
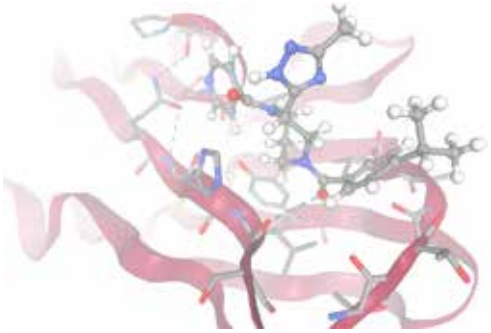
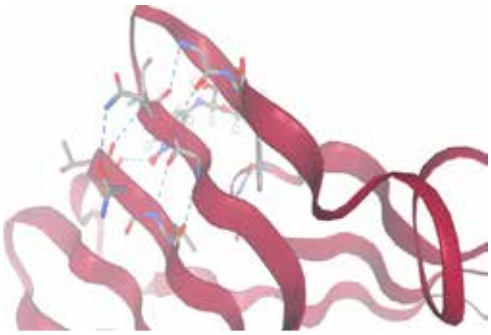
3.2.2 Drug Test (SwissDock)

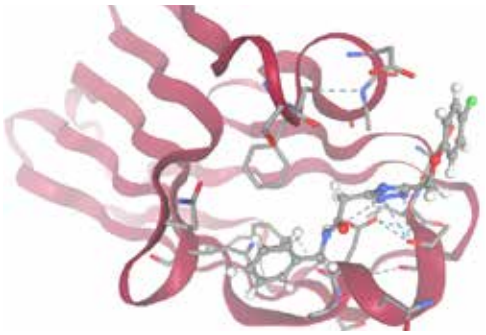
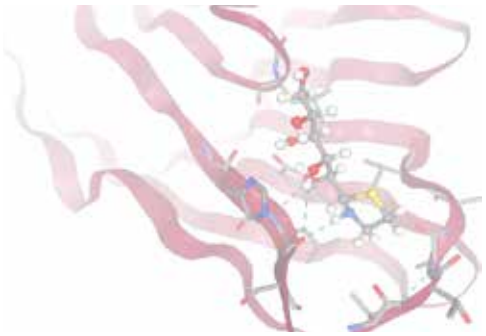
After each drug has finished docking, it generates a list of different sites that it can bond to with TIGIT. Each site is also provided with its SwissParam Score and its AC score. In this experiment, only the site with the lowest SwissParam Score will be used, because the higher the score, the more energy is required for the binding to happen, meaning the lower the level, the reaction will be more spontaneous, happen more easily, and will be used. AC score won't be noted as it isn't necessary. (Table 3) Also, while experimenting, some drugs had to be switched as the SMILES code wouldn't work due to the drugs being more than a single compound, and SwissDock can only take in a single compound.

Table 3. *Information on the 15 drugs' SwissParam score and its best binding location on TIGIT*

Name	SwissParam Score kcal/mol (Lowest)	Binding pose of the compound to TIGIT
Molport-019–897–498	–6.8858	
Molport-051–532–927	–6.7659	
Molport-051–462–100	–6.3235	

Name	SwissParam Score kcal/mol (Lowest)	Binding pose of the compound to TIGIT
Molport-051–454–708	–6.6169	
Molport-051–452–917	–6.7975	
Molport-002–621–450	–6.9804	
Molport-051–470–239	–6.6692	
Molport-020–229–987	–6.5529	

Name	SwissParam Score kcal/mol (Lowest)	Binding pose of the compound to TIGIT
Molport-044–334–503	–7.0876	
Molport-051–517–110	–6.0777	
Molport-046–059–093	–6.6911	
Molport-000–814–864	–5.9198	
Molport-039–048–085	–6.4024	

Name	SwissParam Score kcal/mol (Lowest)	Binding pose of the compound to TIGIT
Molport-005–953–974	–6.8880	
Molport-001–947–650	–5.8708	

3.2.3 Drug Test P. 2 (SwissADME)

After running each drug through SwissADME, the molecular weight, number of hydrogen acceptors and donors, and the CLogP, average LogP score, are noted, as these are the factors required to be checked with Lipinski's Rules. After checking each, the results were that all of the drugs fit the requirements except Molport-001–947–650 (Table 4), which had 6 hydrogen donors, and the limit is 5. Besides this, all other drugs were good for use.

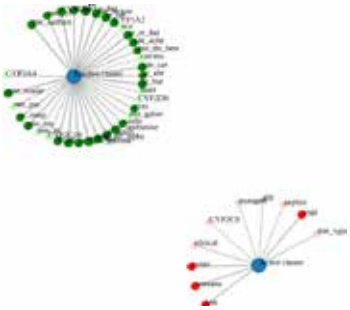
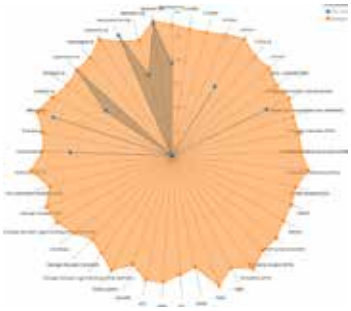
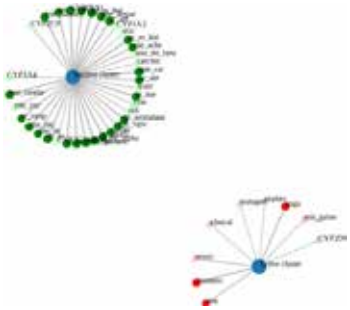
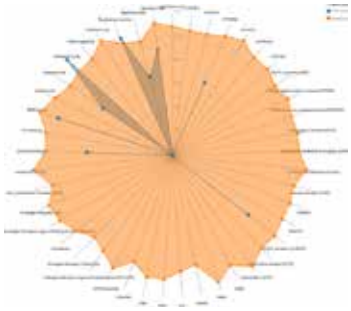
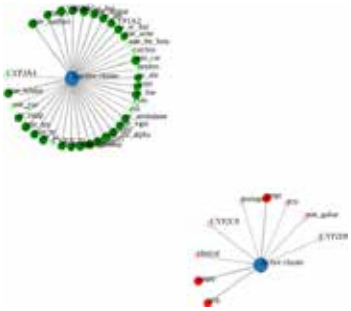
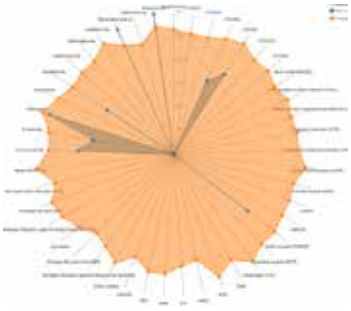
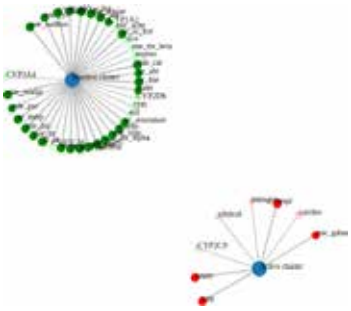
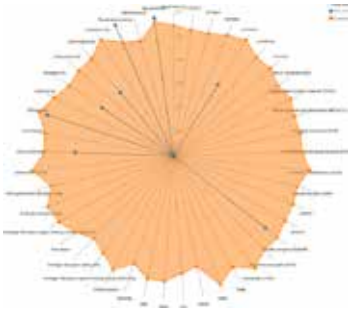
Table 4. *Results of the 15 drugs after SwissADME test, including information on whether it passes or not*

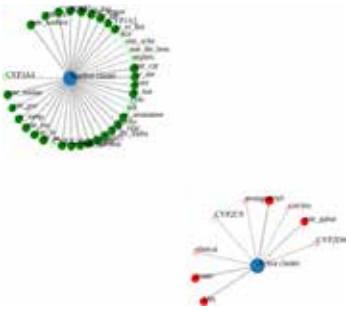
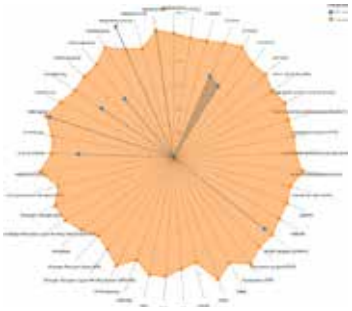
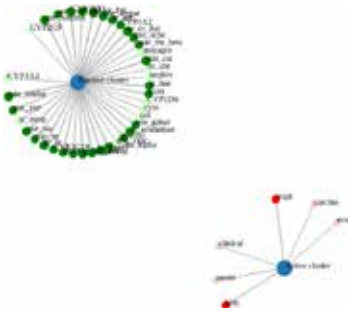
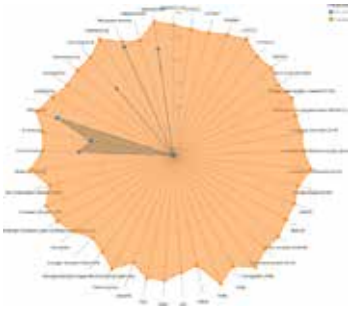
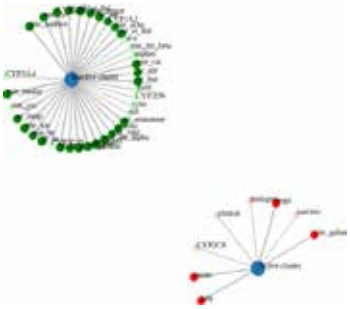
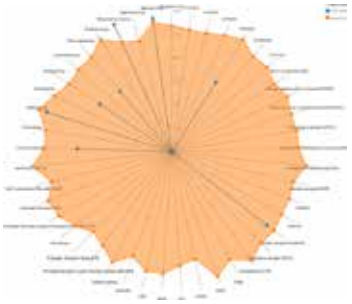
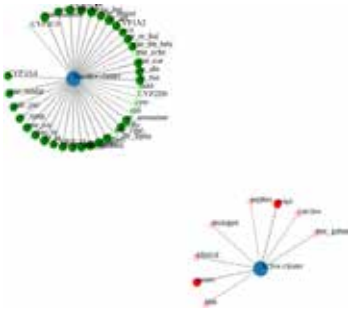
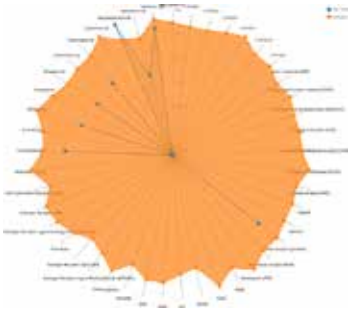
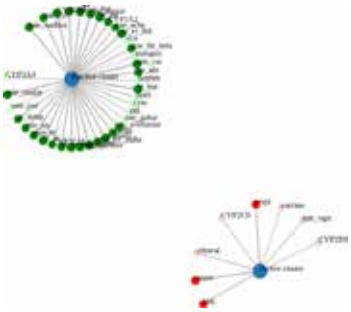
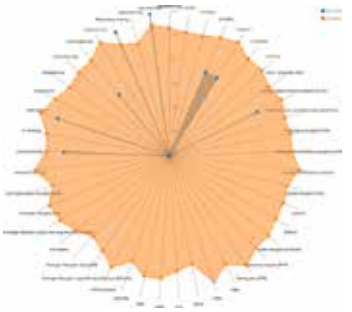
Name	Molecular Weight	Num. H Acceptor	Num. H Donors	CLogP	Agree with Rule
Molport-019–897–498	378.31 g/mol	9	2	2.36	Yes
Molport-051–532–927	328.37 g/mol	6	1	2.03	Yes
Molport-051–462–100	358.79 g/mol	6	1	1.13	Yes
Molport-051–454–708	324.34 g/mol	6	1	0.62	Yes
Molport-051–452–917	338.37 g/mol	6	1	0.94	Yes
Molport-002–621–450	413.52 g/mol	4	3	3.14	Yes
Molport-051–470–239	324.34 g/mol	6	1	0.53	Yes
Molport-020–229–987	343.38 g/mol	6	3	0.19	Yes
Molport-044–334–503	446.43 g/mol	8	2	3.13	Yes
Molport-051–517–110	286.41 g/mol	6	3	0.21	Yes
Molport-046–059–093	432.52 g/mol	5	1	2.45	Yes
Molport-000–814–864	270.24 g/mol	6	4	–0.84	Yes
Molport-039–048–085	265.35 g/mol	4	1	0.99	Yes
Molport-005–953–974	356.81 g/mol	4	2	2.68	Yes
Molport-001–947–650	239.29 g/mol	6	6	–1.71	No

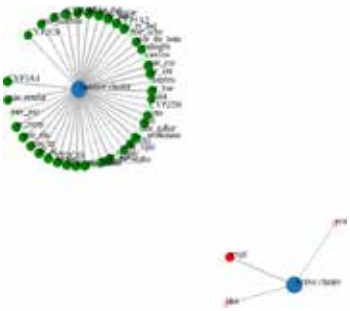
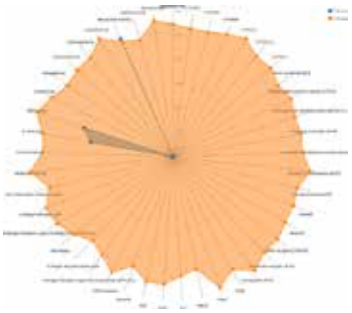
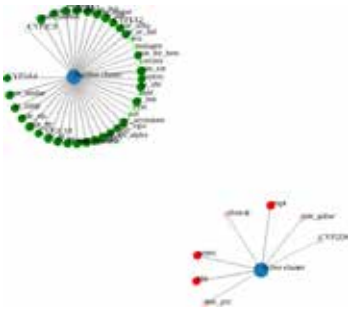
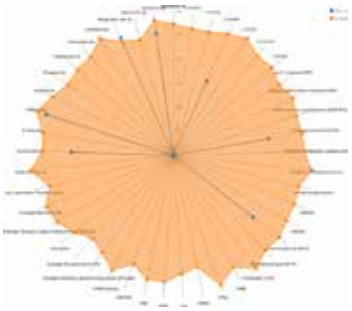
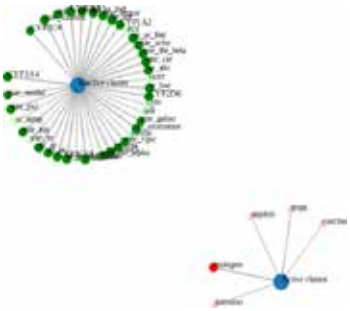
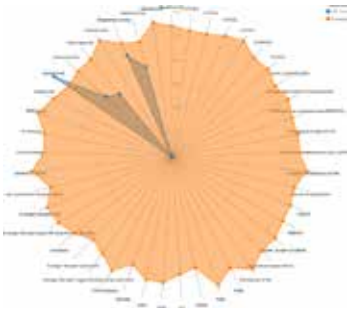
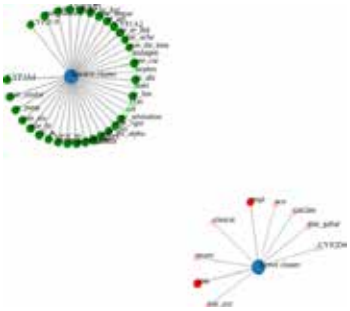
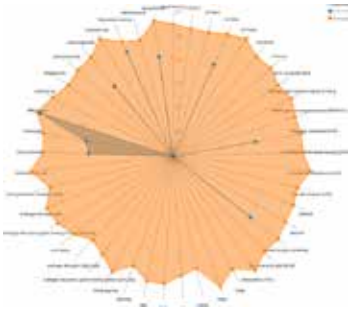
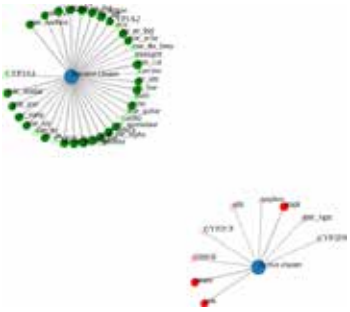
3.2.4 Toxicity Test

Four of the results from the toxicity test will be focused on in this experiment. The Predicted LD50, which is a prediction of how much mg/kg of that substance one would take for a 50% chance of dying, the higher the score, the safer the drug is to the body. In toxicity class, similar to the LD50, the higher score is less toxic, and the lower score is more toxic. Also, every drug is toxic, but this experiment is trying to find out which drugs have a low toxicity so that they wouldn't cause damage to the body when given for TIGIT. The Network Chart shows the toxicity traits of the drug, which is considered safe for the body, along with the toxicity traits that are considered dangerous to the body. Every drug has traits in the dangerous chart.

Table 5. *Results from the 14 drugs' toxicity test. Yellow labels represent the drugs chosen as a result of the experiments*

Name	Predicted LD50	Toxicity Class	Network Chart	Toxicity Radar Chart
Molport-019–897–498	1000mg/kg	4		
Molport-051–532–927	4000mg/kg	5		
Molport-051–462–100	540mg/kg	4		
Molport-051–454–708	540mg/kg	4		

Name	Predicted LD50	Toxicity Class	Network Chart	Toxicity Radar Chart
Molport-051–452–917	635mg/kg	4		
Molport-002–621–450	1500mg/kg	4		
Molport-051–470–239	1100mg/kg	4		
Molport-020–229–987	3500mg/kg	5		
Molport-044–334–503	1000mg/kg	4		

Name	Predicted LD50	Toxicity Class	Network Chart	Toxicity Radar Chart
Molport-051–517–110	2500mg/kg	5		
Molport-046–059–093	210mg/kg	3		
Molport-000–814–864	12400mg/kg	6		
Molport-039–048–085	1300mg/kg	4		
Molport-005–953–974	4000mg/kg	5		

The toxicity radar shows the toxicity level of the drug, represented by the blue dot, compared to the level that is the limit for toxicity on the body. In the end, I have selected three drugs, highlighted in yellow, as the final result of the experiments (Table 5).

Although this experiment was ultimately deemed a success, it still had limitations in terms of resources and experimentation. One of the biggest limitations is doing all of the experiments on the computer using machine learning instead of having actual test subjects. Compared to using the computer, having test subjects can result in better accuracy in certain data. Another limitation is that in the experiment, only 15 drugs were tested. During the Pharmacophore experiment, around 20 million different drugs were generated for each hydrogen acceptor and donor combination, meaning in total, more than 100 million different drugs can bind to TIGIT. However, testing all these could take months or up to a year, hence only 15 were selected for this experiment.

Conclusion

Overall, my experiment on finding a possible immune checkpoint inhibitor drug to bind with TIGIT to prevent it from allowing the immune system to attack early detections of cancer cells was a success, as of the 15 drugs I tested passed the requirements to be a possible inhibitor. In the results of the experiment, I selected three of the drugs based on whether they had a decent SwissParam Score, passed Lipinski's Rule, and had a toxicity class high enough that it wouldn't cause other damage to the body if used. The three drugs might not have been the best in specific experiments, but they fit the requirements well in the overall study. This is a successful experiment, as I was able to find at least one drug that follows these criteria to be used for treating TIGIT. Even though this experiment was very successful, there is much more that can be done to expand it. For example, many other drugs resulting from the pharmacophore can also be found in the same procedure to potentially find even better drugs than the ones in this experiment. Another example is using these drugs on human test-subjects for potentially more accurate data, as this experiment involves all computer and machine learning. There are endless plans that can expand this experiment.

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