Trajectories and Comparative Analysis of Compounds that Bind α4β1 and α4β7

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Background

Integrins are a family of α/ β transmembrane heterodimeric adhesion molecule receptors that help cells communicate to each other in the extracellular matrix. In our studies, we are focusing on Integrin α4β1 and α4β7. These integrins are an example of long-range conformational allostery in proteins. These two receptors are expressed on many white blood cells, including subtypes like leukocytes, lymphocytes, monocytes, basophils and eosinophils. When α4β1 is bound to its counter-receptor, VCAM-1, it induces an inflammatory response. Likewise, the binding of α4β7 and MAdCAM-1, causes the specific inflammatory response of T-cell homing to inflamed gut-associated lymphoid tissue.

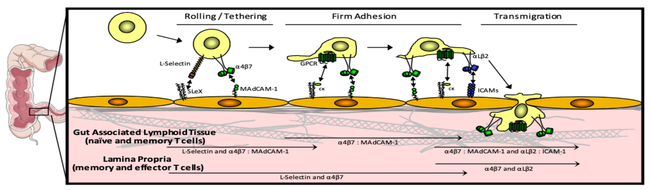

Figure 1

In an effort to provide alternative antibodies targeting a more specific subset of integrins to circumvent JC virus diseases in Natalizumab-directed therapy; Vedolizumab, an α4β7-specific antibody was introduced to clinical trials where it displayed clinical efficacy for remission entrance and preservation in Crohn's disease and ulcerative colitis.

Methodology

The α4β1 and α4β7 models are based on α4β7 (3V4V) and α5β1 (3VI4) crystal structures from the Protein Data Bank. These models are prepared for analysis using the Research Computing Data Core at the University of Houston to run our simulations. Through AUTODOCK TOOLS, we can identify leading pocket-ligand binding poses that then undergo molecular dynamic simulations using GROMACS. The simulations allow us to calculate and analyze clusters, hydrogen bond energies, and contact area to help in the efforts of this research. The simulations are then visualized with PyMOL. The molecular visualization system allows us to hand select important residues that closely interact with leading compounds such as compound x.

Using GRACE, I have post processed plots to further evaluate ligand-pocket binding. These plots show 10 nanoseconds of the distance between pocket and ligand

Results

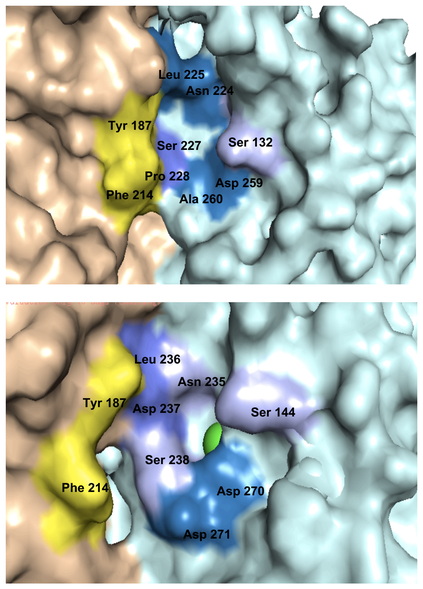

Figure 2: α4β1 model 16 (top), α4β7 model 2 (bottom) residue map

α4β1	α4β7
MG	MG
S132	S144
N224	N235
A260	D271
S227	D237
L235	L236
P228	S238
D259	D270
Y187	Y187
F214	F214

Figure 3: Table list of residues in respect to α4β1 and α4β7

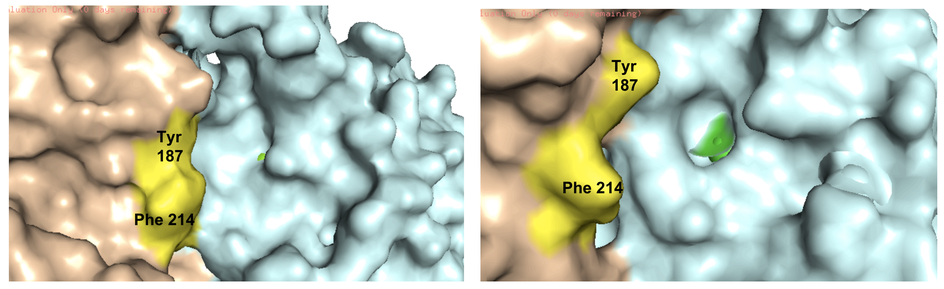

Figure 4: α4β1 model 16 (right) , and α4β7 model 2 (left)

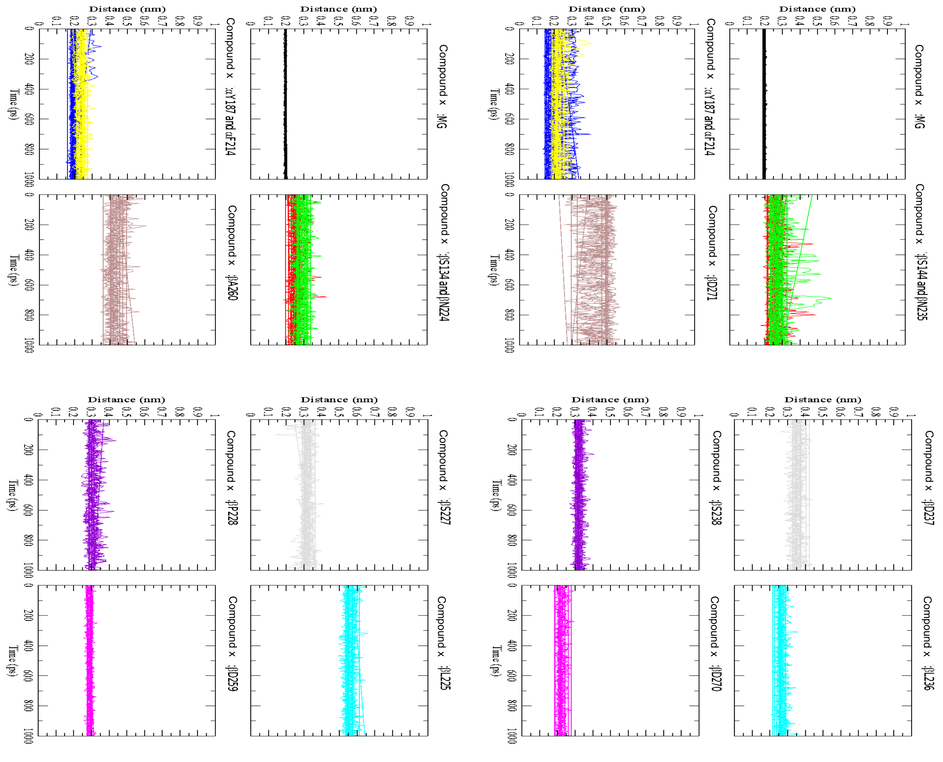

Figure 5: Post processing plots for α4β1 model 16 (right) , and α4β7 model 2 (left)

Conclusions

- The goal of this research is to create a a once-a-day pill that can treat Crohn's Disease and Ulcerative Colitis. This would be a lot cheaper and more manageable alternative to what is currently available right now. Compound x shows promise as, seen from the plots, shows stability and affinity to the pockets of α4β1 and α4β7.
- Compound x seems to have a stronger affinity to the α4β7 pocket as its distance from specific residues were closer during the 10 nanoseconds when compared to the α4β1 pocket.

References

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