The Impact of the Observable Amino Acid Divergence in Late Visit Clones.

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HIV and Infection

- Pathogenesis begins at the biochemical level.
- The gp120 complex interacts with CD4 which T-cell surface glycoprotein and this is the primary method that HIV infects the host.
- A secondary effect of the binding of gp120 to CD4 on the cell surface may also lead to CD4 cell depletion by compromised immune targeting, and may interfere with general CD4 cell function and ontogeny.

Outline

- Markham et al. studied the gp120 & the V3 region within to discover the reason for the variability of the virus
- Scope of the project
- Subject 10 gives the most amount of data points with the most drastic drop in CD4-T cell count.
- Multiple sequence alignment of amino acid and nucleotide sequences reveals disproportionate values for S, theta, min, and max.
- Clones of later visits showed an increased amount of divergence as compared to the original sequence.
- Two non-consensus changes were found on the face of the protein, while the other four non-consensus changes were on the interior of protein
- Single amino acid sequence changes could lead to large conformational changes within the structure of V3

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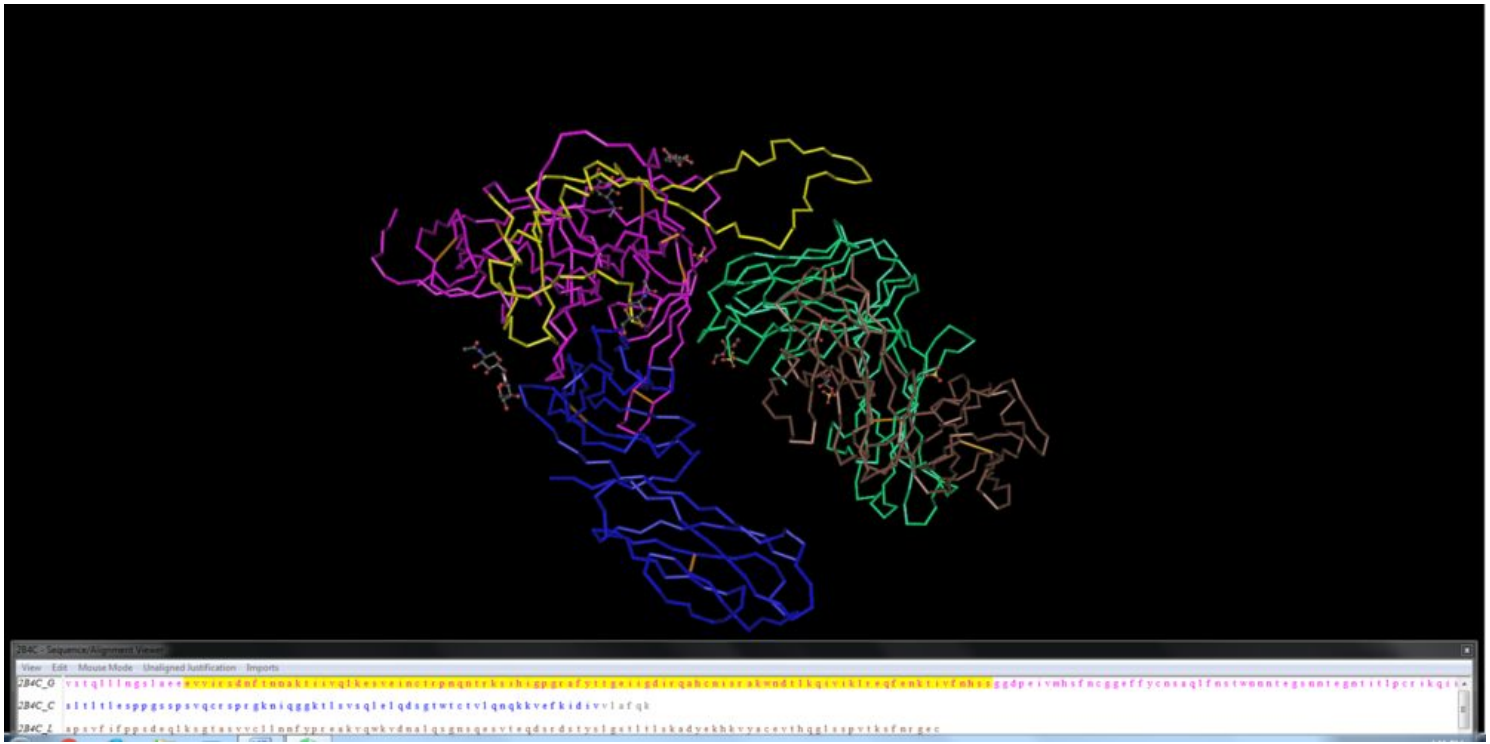
Markham et al. studied gp120 and the V3 Region



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Research Direction

Question: What are the visible protein sequence changes that coexist with a decline in CD4-T cell count and how are those changes altering the characteristics of the amino acid sequences?

Hypothesis: Given that the amino acids of the clones of subject 10 are changing simultaneously within the V3 loop and gp120 contact surfaces which are significant in immune system interaction, there will be a relationship of those regions with the HIV population's perpetuated immunogenicity.

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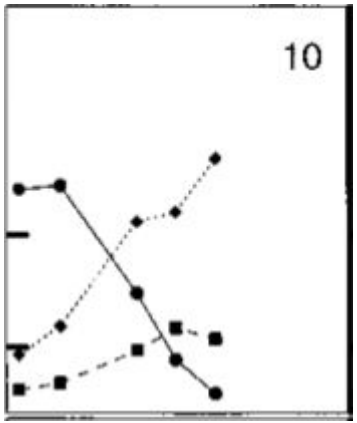
Subject 10 shows a drastic drop in CD4-T cell count with a large increase in diversity

- Subject 10 recorded “6” visits with a total of 49 clones.
  - Part of the rapid progressor group
- The change in condition in the subject suggests an amino acid composition change.



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A Change in DNA Sequence Doesn't Ensure Amino Acid Sequence Change

	Subject	# Clones	S	θ	Min	Max
Amino Acid	10	50	13	8.55	1	15
Nucleic Acid	10	50	74	48.65	1	21

Nonsynonymous vs. Synonymous mutations

- Mutations within genetic information have an immediate effect (A for a G, C for a G) etc. and those changes are carried into the next generation.
- The proteins that those sequences code far may not necessarily be affected.
- Not every mutation occurs in the transcriptional regions for proteins
- Furthermore, if a change does occur it is not guaranteed to greatly influence the final appearance or function of a protein and subsequently any interactions that protein will have.

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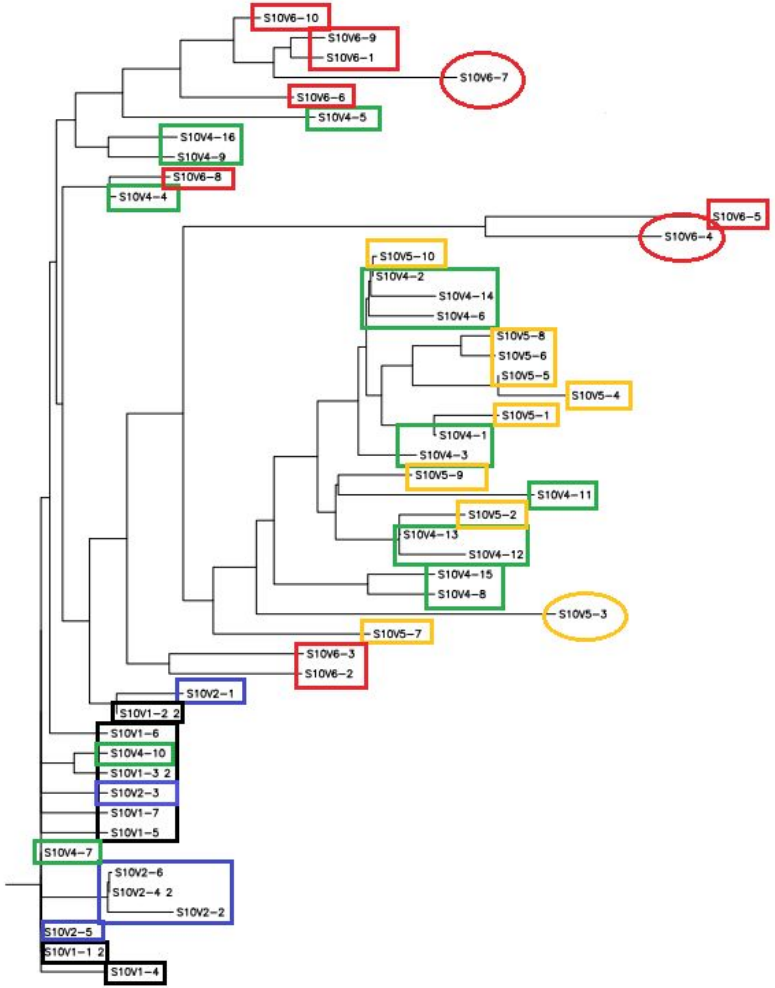
S10V5-3, S10V6-4, and S10V6-7 showed the highest divergence.

- When compared to the original strain these select samples showed the highest changes in their amino acid sequences.
- This was discovered through the CLUSTALDIST program highlighting where the intersections of individuals showed the most divergence.



Based on amino acid sequence

Black: Visit 1
Blue: Visit 2
Green: Visit 4
Yellow: Visit 5
Red: Visit 6

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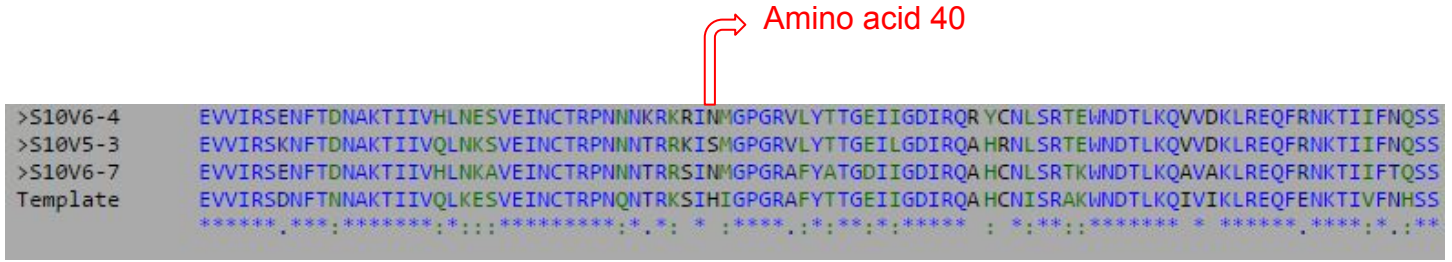
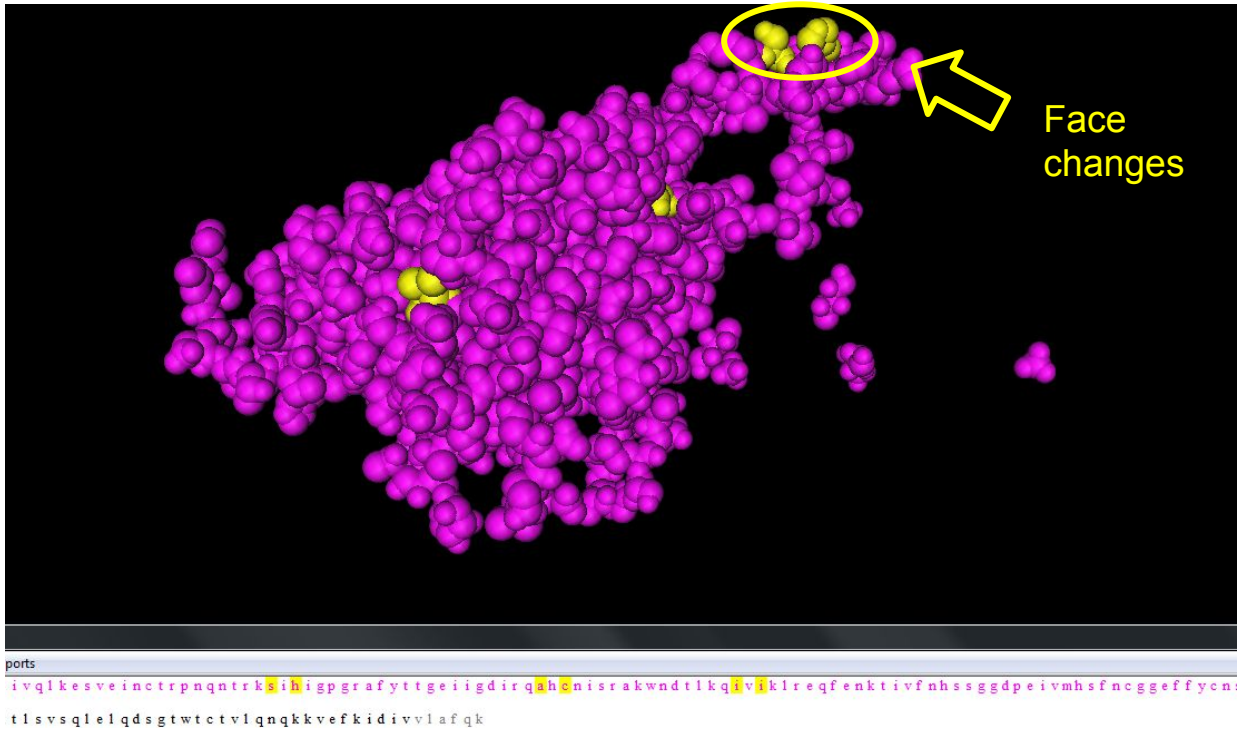
Six non-consensus changes shown in the multiple sequence alignment

- There were several amino acids that could have a large impact on the immunogenicity of HIV given that these changes occurred on the immunogenic tip and the surface of gp120.
- Amino acid 38 & 40 were on the face of the immunogenic tip.
- Amino acid 40 changed from a positively charged histidine in the template to being a polar uncharged amino acid in the three Markham et al. clones.



Six non-consensus changes to the amino acid sequences highlighted in 3D plot



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Future Work

- What is the importance of the change of the positive histidine to polar uncharged amino acids on the immunogenic tip?
- Potentially map the three “largest” changes in other subjects with Subject 10’s plot on the 3D rendering.
- Research variabilities of the other subtypes to compare them to what was found in this study.

Summary

- Markham et al. investigated the gp120 & the V3 region to understand some of the variability of that region.
- Subject 10’s clones were hypothesized to show that critical amino acid changes would influence CD4-T cell decline.
- There were 6 non-consensus changes found, 2 of which having direct interaction with the environment.
- As the experiment progressed divergence of the clones increased from visit to visit.
- Those amino acid changes have the capacity to change the conformation of the protein in discrete and major ways.

Acknowledgments

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- LMU Department of Biology
- Classes of 2017 and 2018

References

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