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Lymphoma: Potential Viral Antagonism between HTLV-1 and JCV Associated with Increased Survival Time

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Abstract

This paper points to a potential antagonism between Human T-lymphotropic virus 1 (HTLV-1) and John Cunningham virus (JCV). Similarities between HTLV1 protease and JCV capsid protein, when compared in silico, offer a possibility of an interaction between the two viral proteins which could influence lymphoma survival rates and the risk of developing this disease.

Introduction

Leukemia and lymphomas are cancers of white blood cells, distinction being in the type of tissue they originate from. In both leukemia and lymphoma, T-lymphocytes and/or B-lymphocytes are commonly affected. Adult T-cell leukemia (ATLL) is associated with Human T-cell Leukemia (Lymphoma) Virus (HTLV1), a retrovirus sharing many similarities with HIV1. While both retroviruses infect the T lymphocytes, HTLV1 can also infect other cell types [1]. HIV1 and HTLV1 differ in their pathogenic mechanisms: HIV1 induces death of CD4 lymphocytes, leading to AIDS, while HTLV1 transforms the lymphocytes into cancer cells via its Tax protein, leading to leukemia or lymphoma [2]. Tax deregulates multiple signaling pathways, promoting cell proliferation and inhibiting apoptosis [3]. HTLV1 has also been found to transform B-lymphocytes, suggesting its potential role in B-cell lymphomas [4].

The polyproteins of HIV1 and HTLV1 show significant similarities. So it is no surprise that HIV1 inhibitors have been found to also inhibit HTLV1 enzymes, for example HIV1 protease inhibitors, darunavir and indinavir, showed strong inhibition of HTLV1 protease. [5].

Main content

A study assessing HTLV1 prevalence in non-Hodgkin's lymphoma (NHL) patients found HTLV1 in 18.8% of samples, conclusion being that NHL patients should be screened for and treated against this virus [6]. Another study explored prevalence of polyomaviruses, JCV and BKV, in lymphoma patients, revealing a higher survival rate in those patients with detected polyomaviral DNA in serum [7]. JCV antibodies were also more prevalent in the healthy control group compared

to NHL patients, 59% of control group had antibodies to JCV detected, in comparison 49% of NHL patients had antibodies to JCV detected [8].

Comparative analysis of JCV and HTLV1 proteins with BLAST showed short peptide alignments, indicating potential similarities. Best alignment was between JCV capsid protein and HTLV1 polyprotein:

Query: Capsid protein [JC polyomavirus type 3], accession number: 4X0Y_A
Subject: Pr gag-pro [Human T-cell leukemia virus type I], accession number: NP_057861.1

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Expect: 0.19
Identities: 19/71(27%), Positives: 29/71(40%), Gaps: 13/71(18%)

Query   129  VGGEALE-LQGVVFNYRTTYPDGTIFPKNATVQSQVMNTEH--------KAYLDKNKAYP  179
             +G +AL+  QGV++       P   I P  A     V+  EH        +  L++N + P
Sbjct   550  IGRDALQQCQGVLYLPEAKRPP-VILPIQAPA---VLGLEHLPRPPEISQFPLNQNASRP  605

Query   180  VECWVPDPTRN  190
                W   P R
Sbjct   606  CNTWSGRPWRQ  616
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In the HTLV1 polyprotein, aminoacid sequence from 459 to 563 is an aspartate protease whose function is to split the retroviral polyproteins into functional parts.

Alignment sequence between JCV VP1 capsid protein and HTLV1 polyprotein overlaps with the aminoacids of HTLV1 protease, so we will compare the JCV capsid protein with HTLV1 protease further.

Crystal structure of HTLV1 protease (method X-ray diffraction) is taken from RCSB Protein Data Bank[9][10], and same for the crystal structure of JC polyomavirus VP1 capsid protein [11][12].

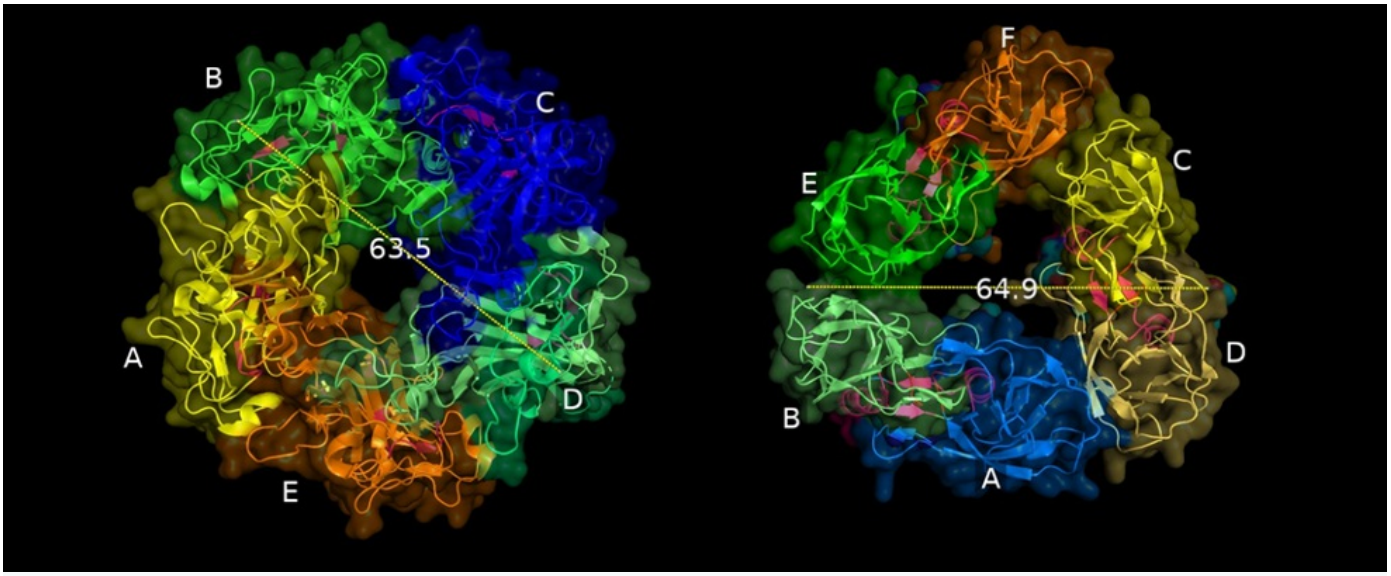


Figure 1. Left is JCV capsid protein VP1 consisting of five identical chains (A, B, C, D, E). Right is HTLV1 protease consisting of six identical chains

(A, B, C, D, E, F).

Both proteins form a ring like structure with their identical chains, JCV capsid VP1 with five chains, and HTLV1 protease with six chains. From the top view, the diameter of the surface of the ring is between 60 and 70 Å for both proteins.

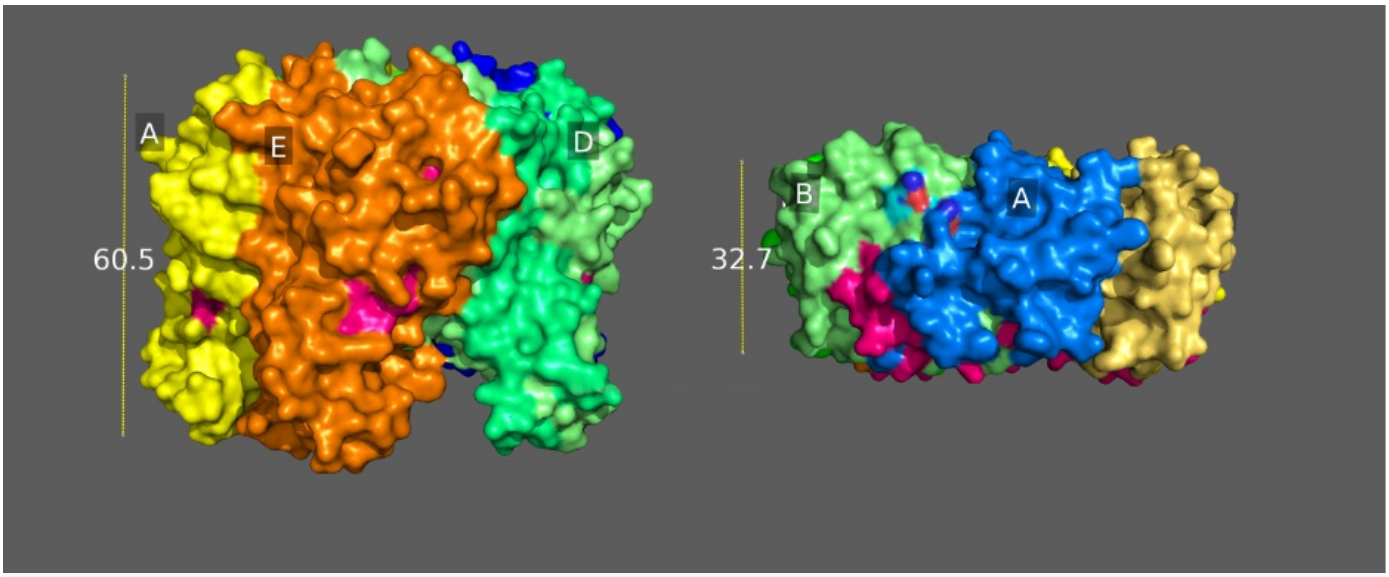
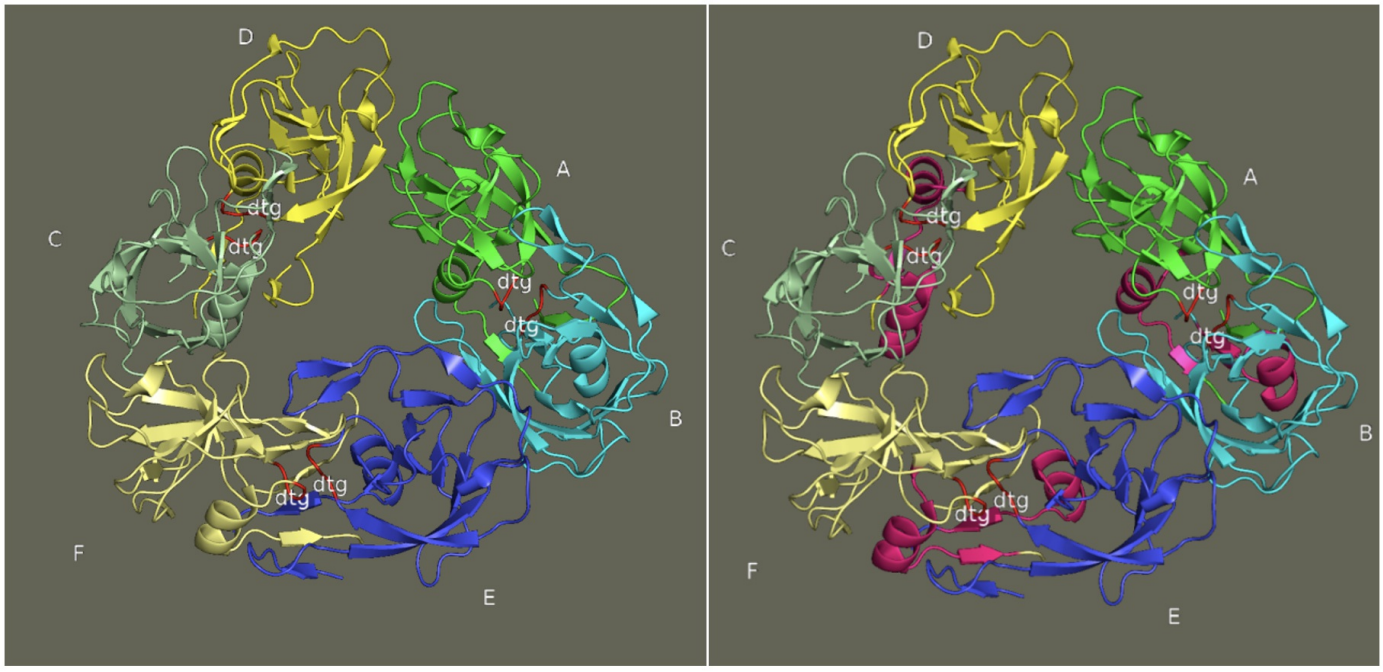


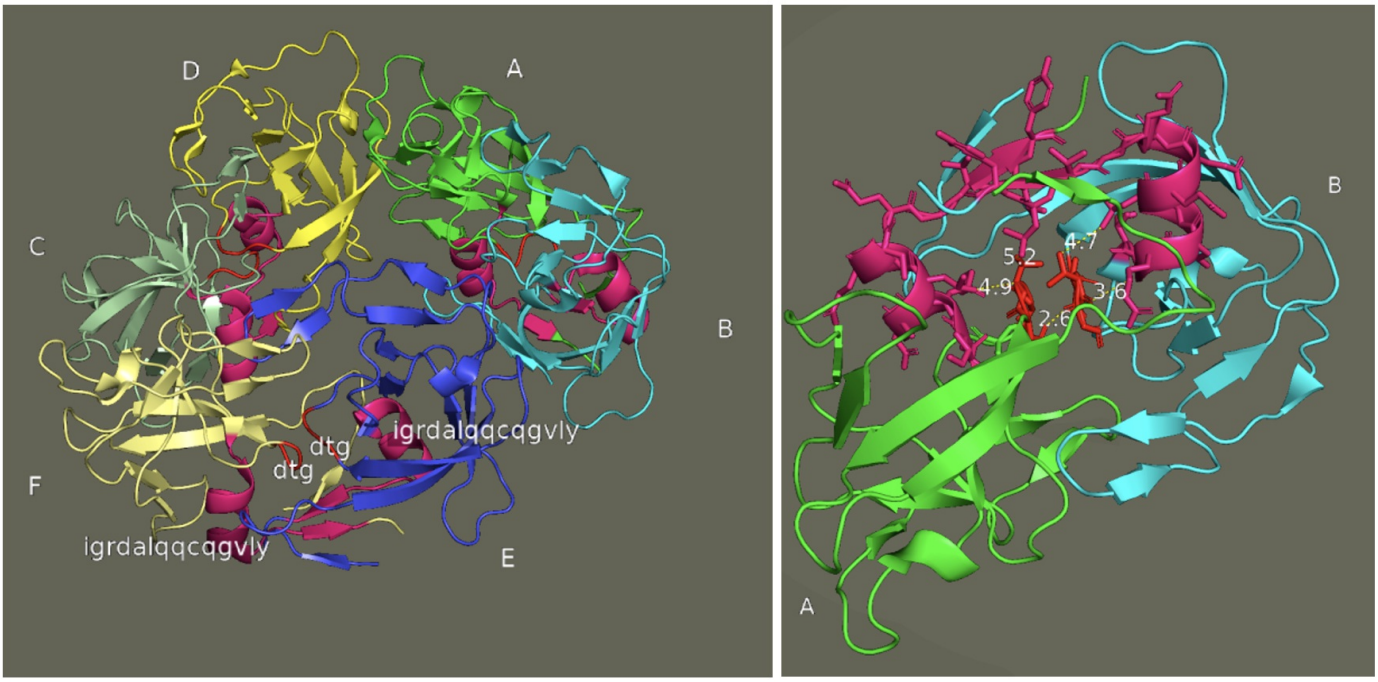
Figure 2. Side view of the proteins. Left is JCV capsid protein VP1. Right is HTLV1 protease. Alignment sequences on both proteins are marked purple.

From the sideview, JCV VP1 capsid protein is around two times longer than HTLV1 protease. That is because the chains of VP1 that form the ring are longer than chains of HTLV1 protease (272 aa compared to 116 aa).



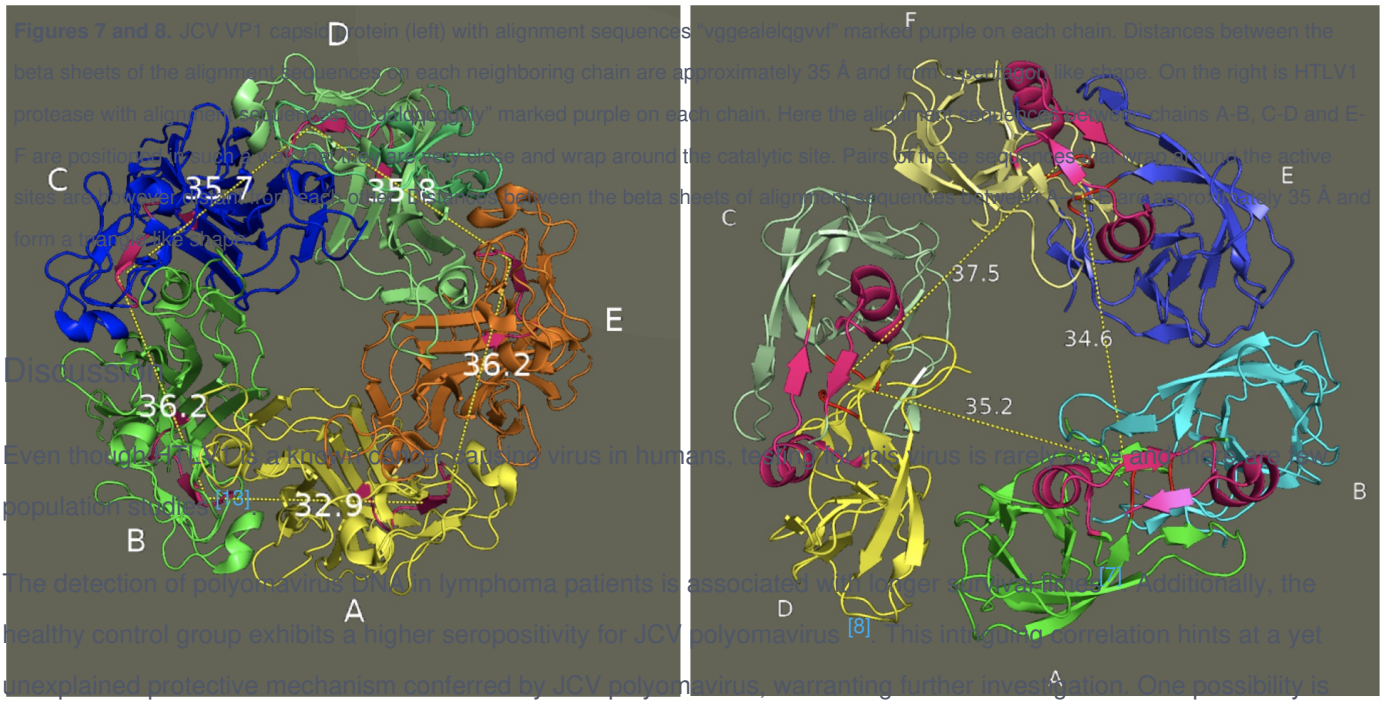
Figures 3 and 4. HTLV1 protease has a catalytic sequence “dtg” on each protein chain that creates the active site. It is marked with red color (left)

and we can see that two neighboring chains (A – B, C – D, E – F) have their “dtg” motifs next to each other and so the active site is created by repeating motifs between neighbor chains. On the right, the “igrdalqqcqgvly” alignment sequence is marked purple on each chain and we can see that it is close to the “dtg” active site and surrounds it.



Figures 5 and 6. HTLV1 protease and its active sites surrounded by the alignment sequences (left). On the right is a closer view of the active site between chains A and B of HTLV1 protease. Aminoacids of the catalytic motifs (“dtg”) between the chains are less than 3 Å apart, and aminoacids belonging to the sequence that aligns with the JCV VP1 capsid protein are less than 5 Å apart from the catalytic motif.

The alignment sequence on the HTLV1 protease undoubtedly interacts with the active site of the HTLV1 protease.



Figures 7 and 8. JCV VP1 capsid protein (left) with alignment sequences "vggealelqgvvf" marked purple on each chain. Distances between the beta sheets of the alignment sequences on each neighboring chain are approximately 35 Å and form a triangle like shape. On the right is HTLV1 protease with alignment sequences "vggealelqgvvf" marked purple on each chain. Here the alignment sequences between chains A-B, C-D and E-F are positioned in such a way that they are close to the active site and wrap around the catalytic site. Pairs of these sequences wrap around the active sites and show several main interactions between the beta sheets of alignment sequences between chains A-B, C-D and E-F are approximately 35 Å and form a triangle like shape.

virus antagonism between HTLV1 and JCV.

The 3D structures of JCV VP1 protein and HTLV1 protease show several similarities, main ones being: similar diameter of the protein ring surface (approximately 65 Å), similar number of identical aminoacid chains creating a quaternary structure, aligned sequences create a beta sheet secondary structure in both proteins, distances between the aligned beta sheets between neighboring chains in both proteins are approximately 35 Å.

Aligned sequences in HTLV1 protease wrap around the catalytic site and affect it due to closeness of the aminoacid residues and the active site.

Because of the similarities in structure and the similarity of the short aligned sequences, it is possible the two proteins have similar enough epitopes that an antibody raised against one protein could also recognize and bind to the other protein. This phenomenon is known as cross-reactivity [14].

Another possibility is interference between the two similar proteins during virus assembly. For example JCV capsid proteins might bind the HTLV1 protease during capsid self-assembly because capsids of polyomaviruses can integrate their proteins in many different spatial configurations [15]. JCV capsid protein competing with HTLV1 protease for the protease substrate could also be the case.

To test these theories several experiments need to be designed. For virus antagonism in vitro, cell cultures co-infected with HTLV1 and JCV compared to control groups infected with just HTLV1 and JCV separately can be observed, and in case of antagonism viral titration should be lower in the co-infected cultures.

To test inhibition of HTLV1 protease with JCV VP1 capsid protein, activity of HTLV1 protease can be tested with JCV VP1 present compared to its activity where JCV VP1 is not present.

To test binding of HTLV1 protease with JCV capsid, a marked HTLV1 protease or HTLV1 polyprotein can be mixed with JCV infected cell cultures and then observed, after JCV purification, if it was incorporated into the capsid.

Finally for the antibody cross reactivity, antibodies raised against JCV capsid proteins can be tested on HTLV1 polyprotein or HTLV1 protease.

Perhaps more importantly, more research should be done regarding HTLV1 and its effect on cancer considering if the inhibition of HTLV1 by JCV is proven true and does effect increased survival of lymphoma patients then inhibition of HTLV1 by antiretroviral drugs would also have a positive effect on survival.

Conclusion

Understanding the connection between viruses and tumors is crucial for cancer treatment. HTLV1, a known lymphoma-causing virus, presents an avenue for potential therapies. Polyomaviruses, contrary to expectations, showed a protective effect against lymphoma in two different experiments. The similarities between HTLV1 protease and JCV capsid protein raise questions about potential antagonistic effects between the viruses or potential enhancement of immune response to HTLV1 due to presence of JCV proteins. These hypotheses require further investigation in controlled conditions for validation.

References

1. ^*Rocamonde, B., Carcone, A., Mahieux, R., & Dutartre, H. (2019). HTLV-1 infection of myeloid cells: from transmission to immune alterations.*
2. ^*Kalinichenko, S., Komkov, D., & Mazurov, D. (2022). HIV-1 and HTLV-1 Transmission Modes: Mechanisms and Importance for Virus Spread.*
3. ^*Mohanty, S., & Harhaj, E. W. (2020). Mechanisms of Oncogenesis by HTLV-1 Tax.*
4. ^*Dan L. Longo, Edward P. Gelmann, Jeffrey Cossman, Rebecca A. Young, Robert C. Gallo, Stephen J. O'Brien & Louis A. Matis (1984) Isolation of HTLV-transformed B-lymphocyte clone from a patient with HTLV-associated adult T-cell leukaemia*
5. ^*Kassay, N., Mótyán, J. A., Matúz, K., Golda, M., & Tozsér, J. (2021). Biochemical Characterization, Specificity, and Inhibition Studies of HTLV-1, HTLV-2, and HTLV-3 Proteases.*
6. ^*Maryam Rastin, Ali Reza Khoee, Nafiseh Tabasi, Akram Sheikh, Saeed Ziaolhagh, Elham Esmaeeli, Shahrzad Zamani, Mahdieh Khazaee, and Mahmoud Mahmoudi (2013) Evaluation of HTLV-I and HCV Prevalence in Non-Hodgkin's Lymphoma*
7. [a, b]*Loutfy, S. A., Moneer, M. M., Salem, S. E., Abada, E. A. E.-M., Ahmed, L. H. I., Ibrahim, L. H., et al. (2017). Polyomavirus infections and its clinical relevance in cancer patients: A Prospective Study.*
8. [a, b]*Engels, E. A., Rollison, D. E., Hartge, P., Baris, D., Cerhan, J. R., Severson, R. K., et al. (2005). Antibodies to JC and BK viruses among persons with non-Hodgkin lymphoma.*

9. ^*https://www.rcsb.org/structure/2B7F*
10. ^*Li, M., Laco, G.S., Jaskolski, M., Rozycki, J., Alexandratos, J., Wlodawer, A., Gustchina, A. (2005) Crystal structure of human T cell leukemia virus protease, a novel target for anticancer drug design*
11. ^*https://www.rcsb.org/structure/4X0Y*
12. ^*Stroh, L.J., Maginnis, M.S., Blaum, B.S., Nelson, C.D., Neu, U., Gee, G.V., O'Hara, B.A., Motamedi, N., DiMaio, D., Atwood, W.J., Stehle, T. (2015) The Greater Affinity of JC Polyomavirus Capsid for alpha 2,6-Linked Lactoseries Tetrasaccharide c than for Other Sialylated Glycans Is a Major Determinant of Infectivity.*
13. ^*Kristien Verdonck, Elsa González, Sonia Van Dooren, Anne-Mieke Vandamme, Guido Vanham, Eduardo Gotuzzo (2007) Human T-lymphotropic virus 1: recent knowledge about an ancient infection*
14. ^*Thomas Dyrberg, Jacob Sten Petersen, Michael B.A. Oldstone (1990) Immunological cross-reactivity between mimicking epitopes on a virus protein and a human autoantigen depends on a single amino acid residue*
15. ^*Adam Zlotnick, Stephen J. Stray (2003) How does your virus grow? Understanding and interfering with virus assembly*