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Anindita Varshneya, Jordan Detamore, Colin Wikholm, Isai Lopez
BIOL 368: Bioinfomatics Laboratory
Department of Biology
Loyola Marymount University
October 25, 2016

Outline

- **HIV-1 infection of host cells involves primary complexing of gp120 with CD4, secondary chemokine receptor binding, and cell fusion.**
- **Understanding conformational changes in complexed viral-cell structures may explain function and possible treatments.**
- **Kwong et al. (1998) studied gp120/CD4/NAb for structural determination and function.**
- **They identified the ternary complex structure, binding interfaces, and modes of immune evasion.**
- **Future studies should analyze other intermediates to address fusion mechanisms, alternate glycoprotein states, and other areas.**

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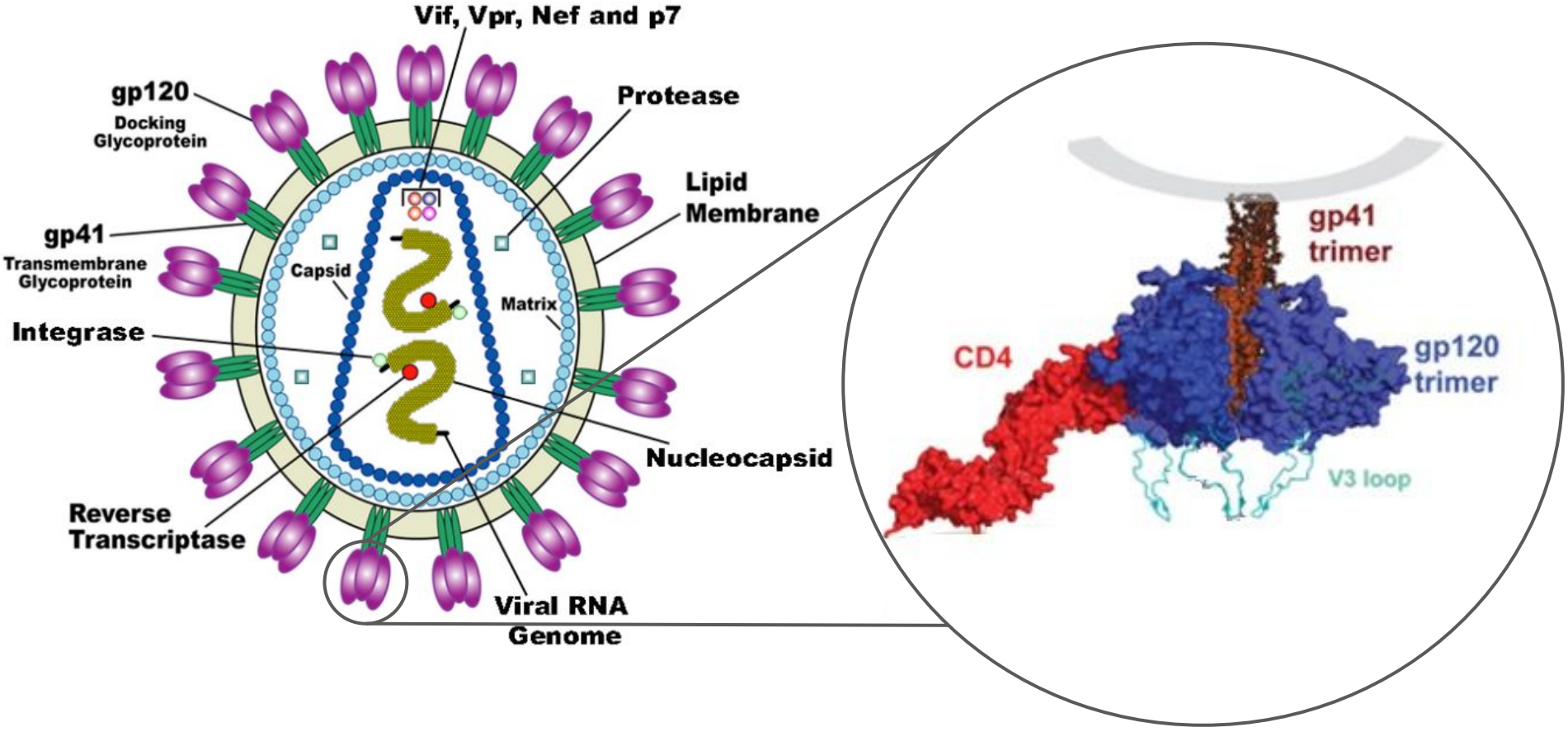
The HIV-1 Expresses a Series of Surface Proteins for Infection of Host Cells

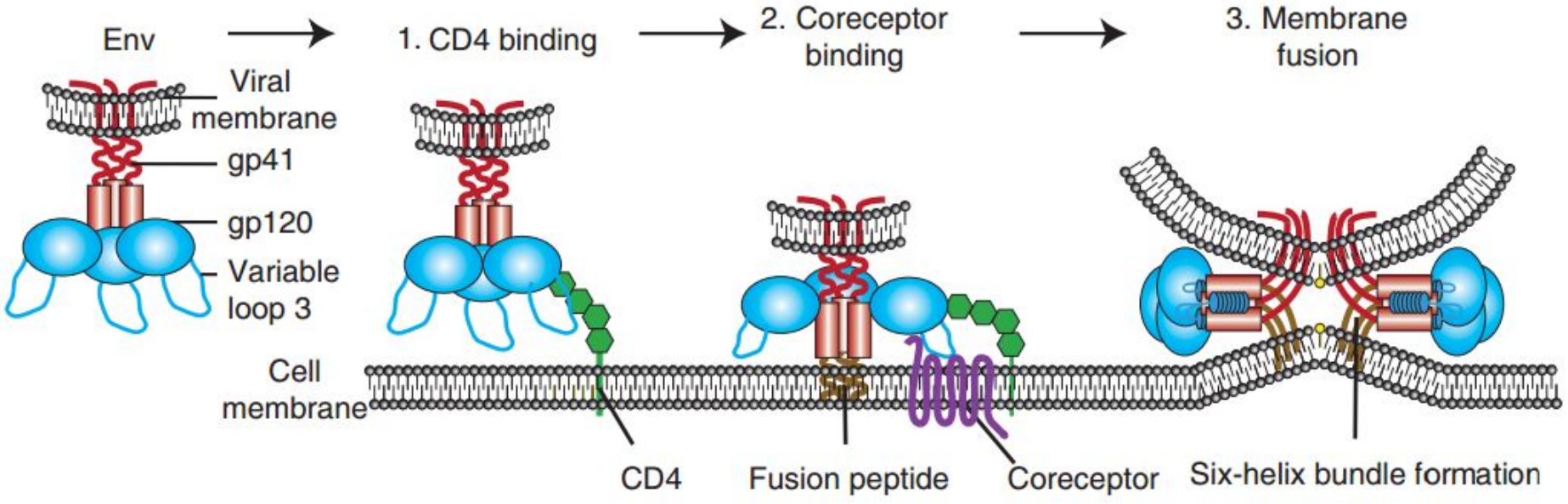
- **The gp160 is cleaved into gp120 and gp41, which together form the viral spike.**



http://people.mpi-inf.mpg.de/~fmueller/thesis/thesis_mueller.pdf

HIV-1 Infection of Host Cell Involves Primary Binding, Secondary Binding, and Membrane Fusion

1. **The gp120 binds to CD4, inducing conformational change in gp120.**
2. **The gp120 binding sites are exposed and CXCR4 binds to gp120.**
3. **The gp41 glycoprotein initiates fusion of virus and cell membranes.**



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3405824/

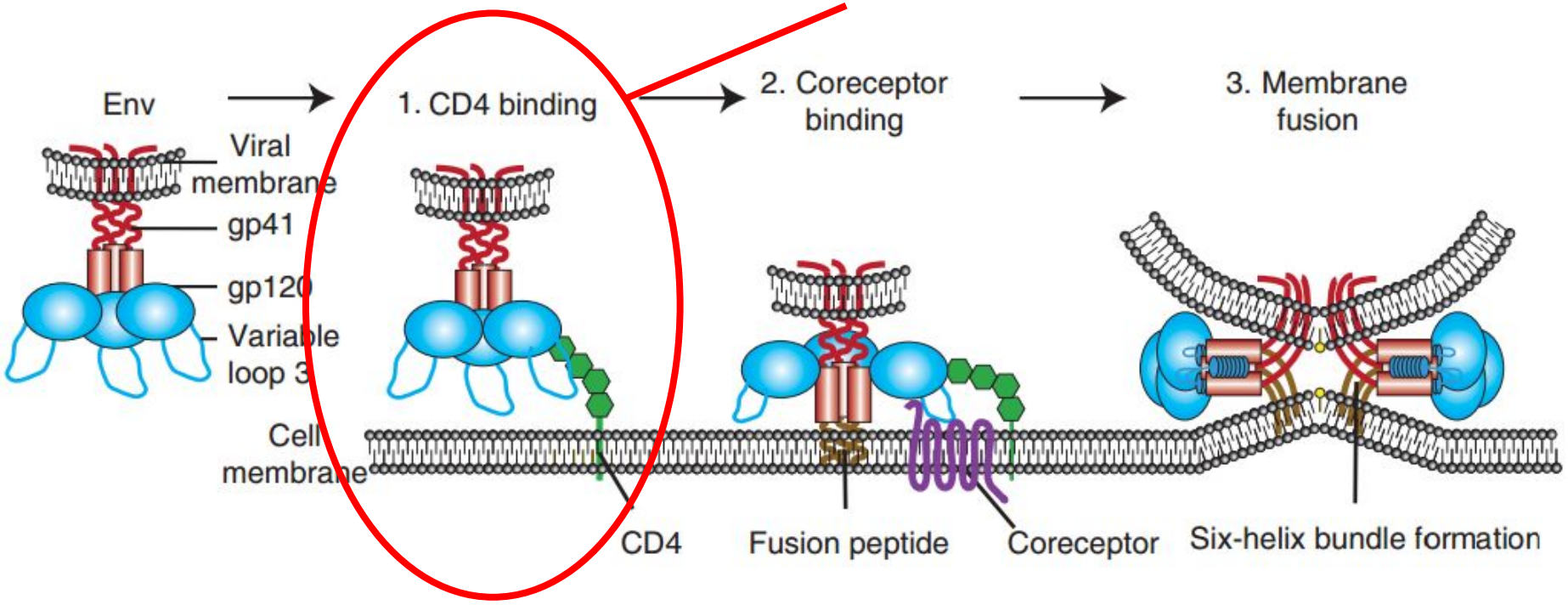
HIV-1 Infection of Host Cell Involves Primary Binding, Secondary Binding, and Membrane Fusion

Leads to chemokine receptor binding

-OR-

Neutralization by CD4i NAb

(CD4 induced neutralizing antibodies)



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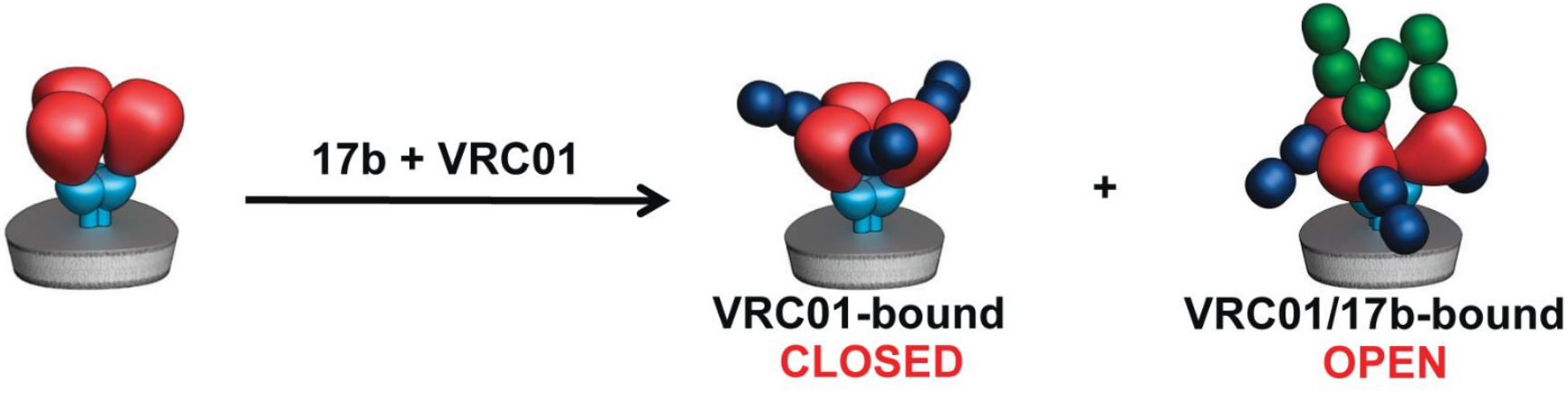
The gp120 binding of CD4 Induces Conformational Changes that Allow for CD4i NAb Binding

- **Structure is important for function.**
  - Understanding the distinctive structures of the tetramer is thus important for understanding function and possible treatments.



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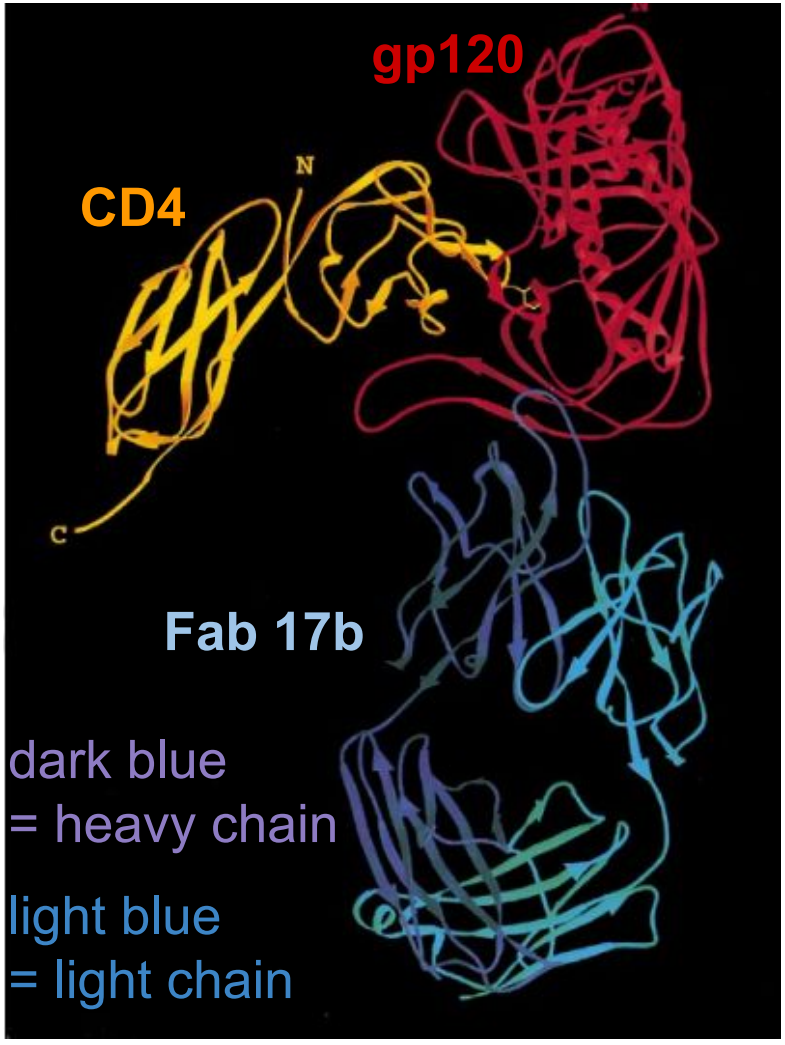
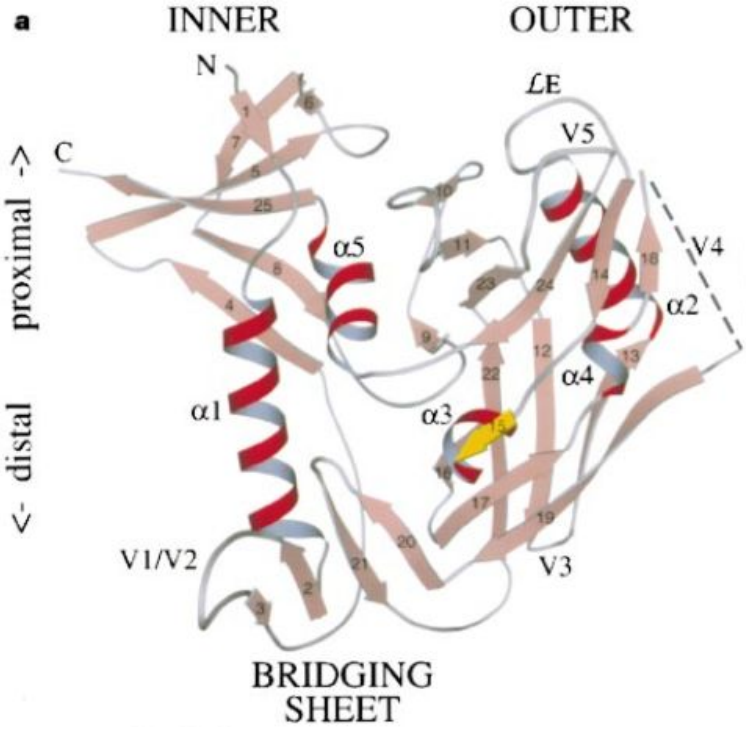
X-ray Crystallography of the gp120/CD4/NAb Complex Allowed for Reliable Modeling of Overall Ternary Structure

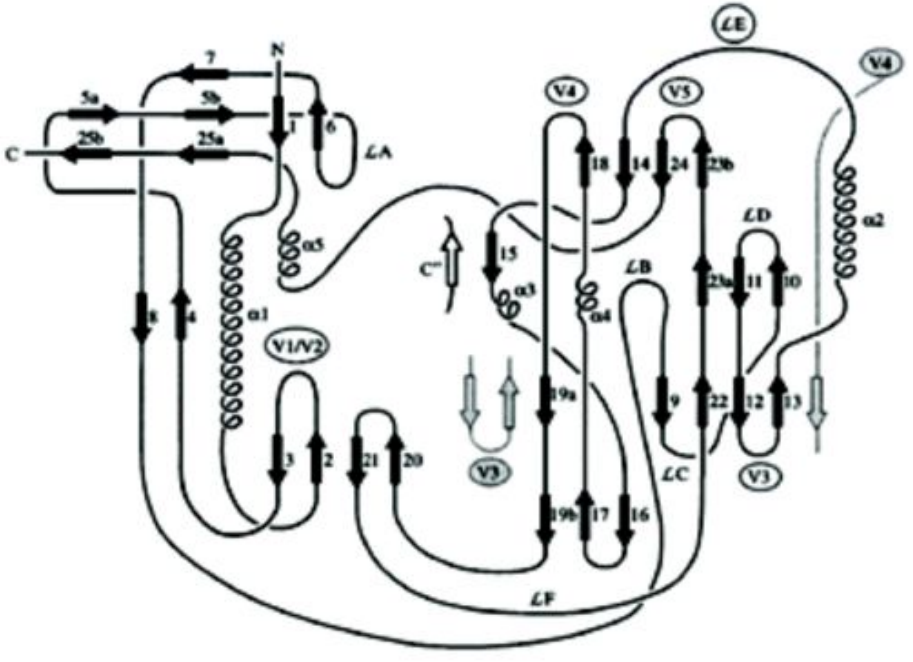
R-value = 21.0% (5–2.5 Å data > 2σ, R-free = 30.3%)



Kwong et al. 1998

Structural Views of the gp120 Protein Indicate Binding Sites for CD4





Kwong et al. 1998

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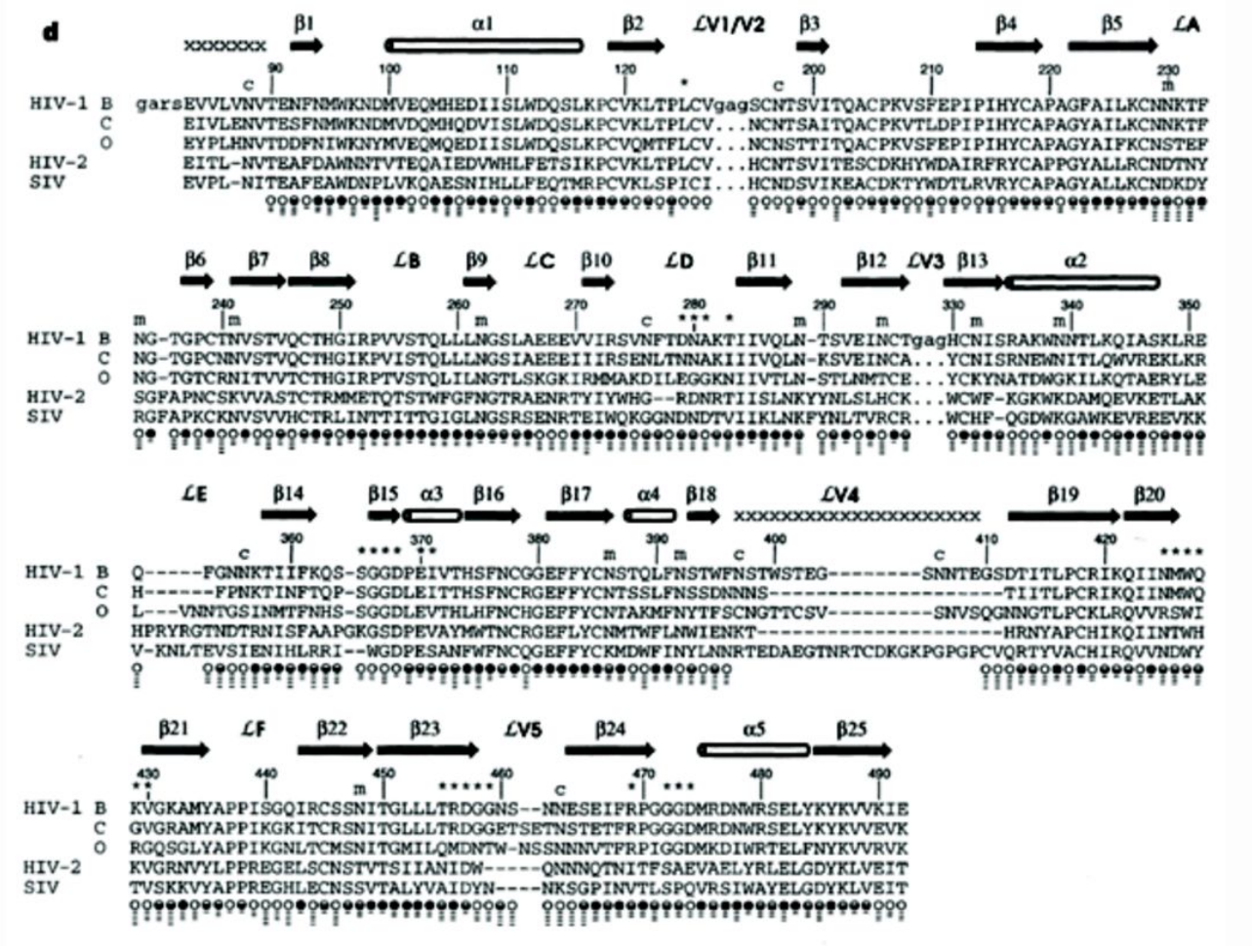
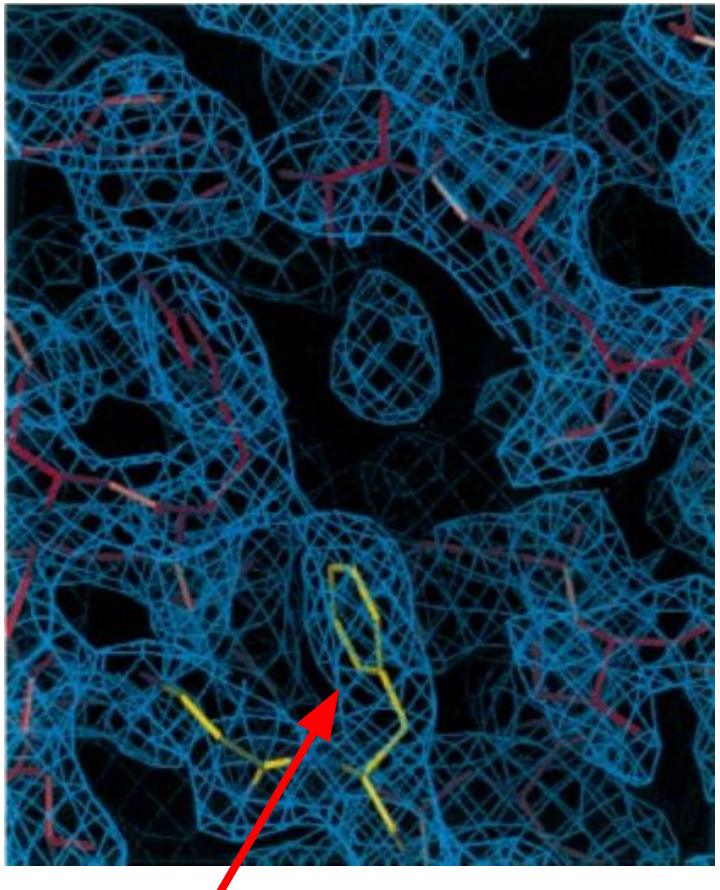
Kwong et al. 1998

Direct Contact Between CD4 and gp120 was Diagrammed Instead of Loss of Solvent-Accessible Surfaces



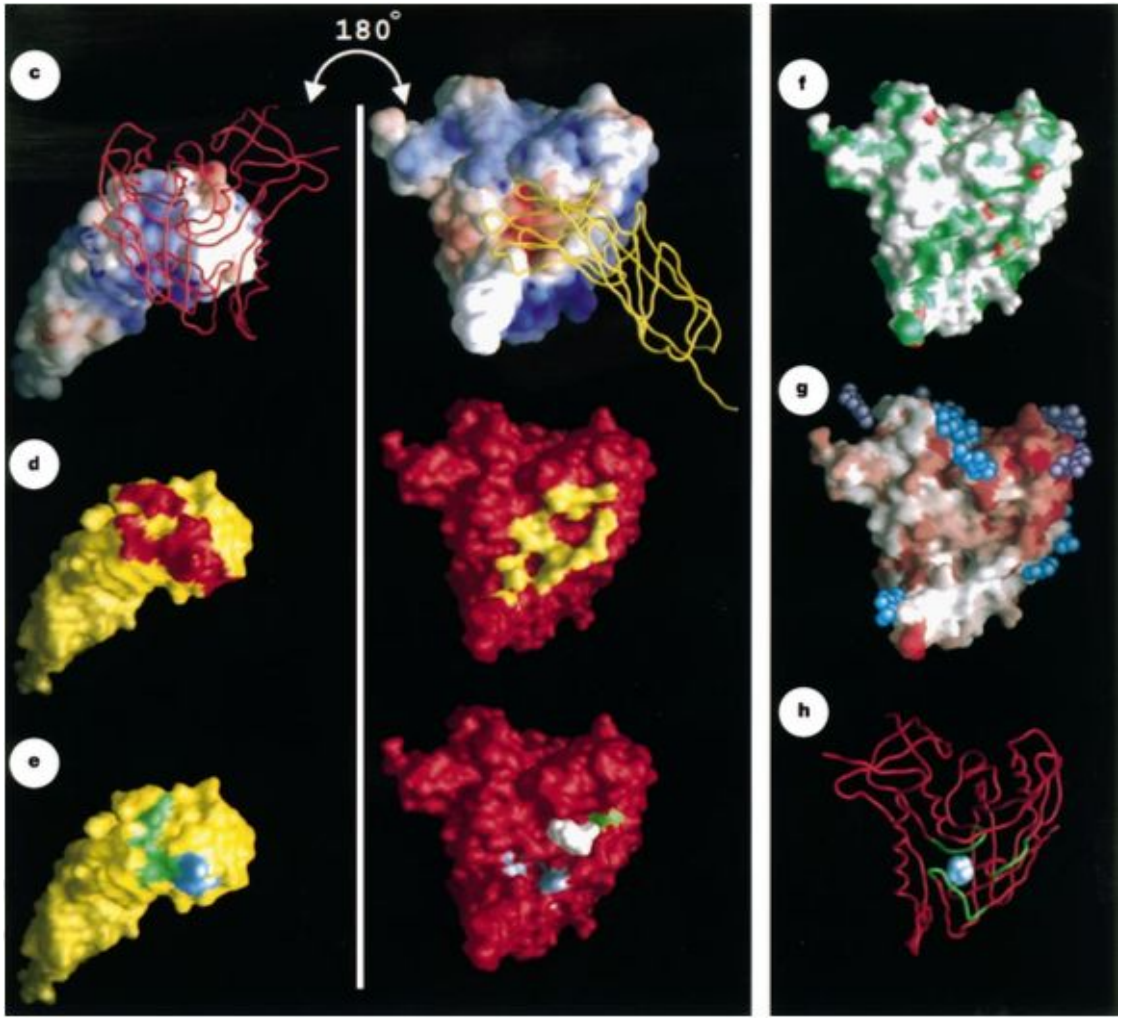
Kwong et al. 1998

The gp120-CD4 Protein Complex Creates a Phe43 Cavity Essential to Viral Entry



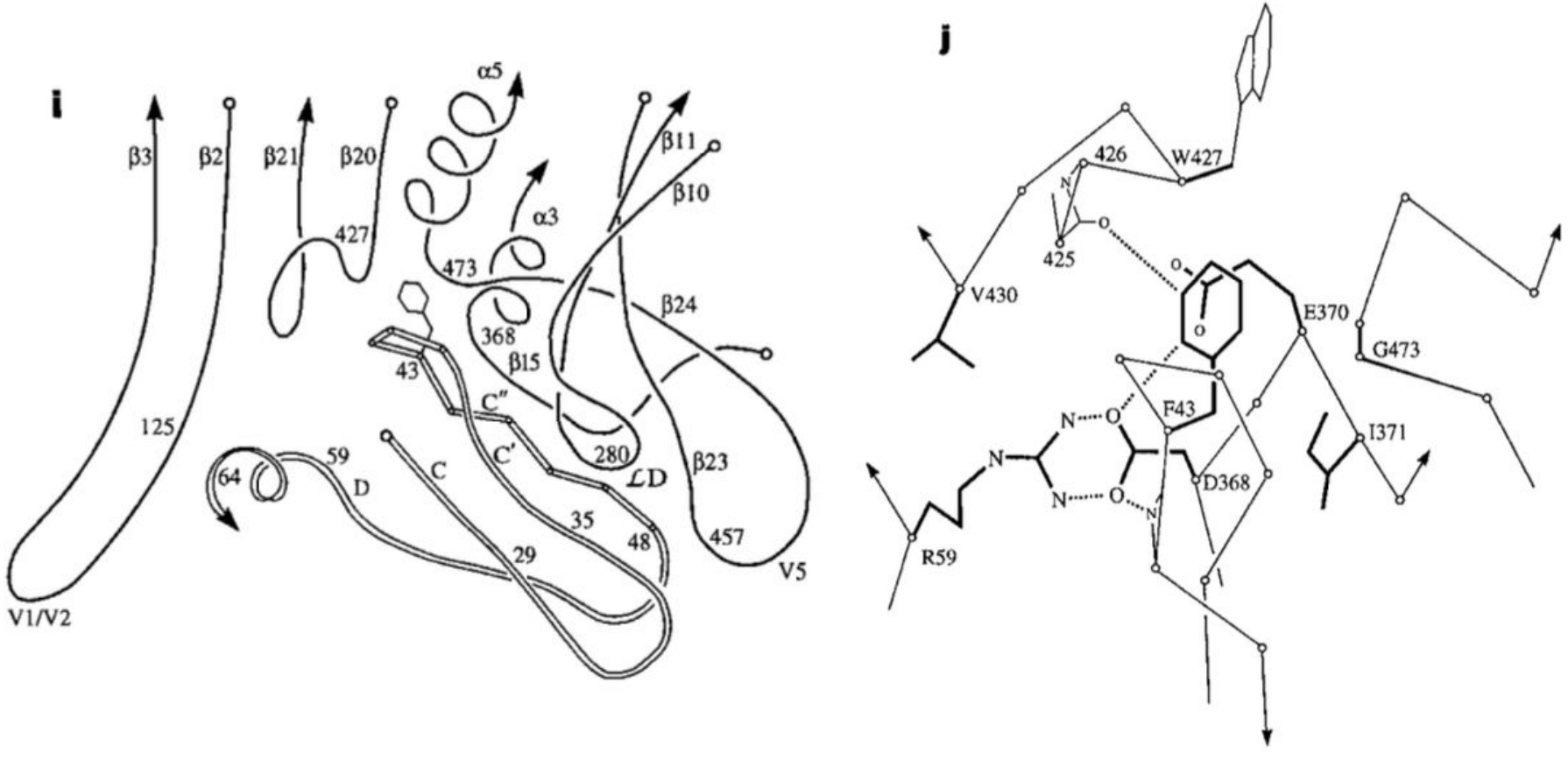
Kwong et al. 1998

The gp120 and CD4 Bind and Cause a Conformational Change That Create a Cavity Near the Phe 43 Residue



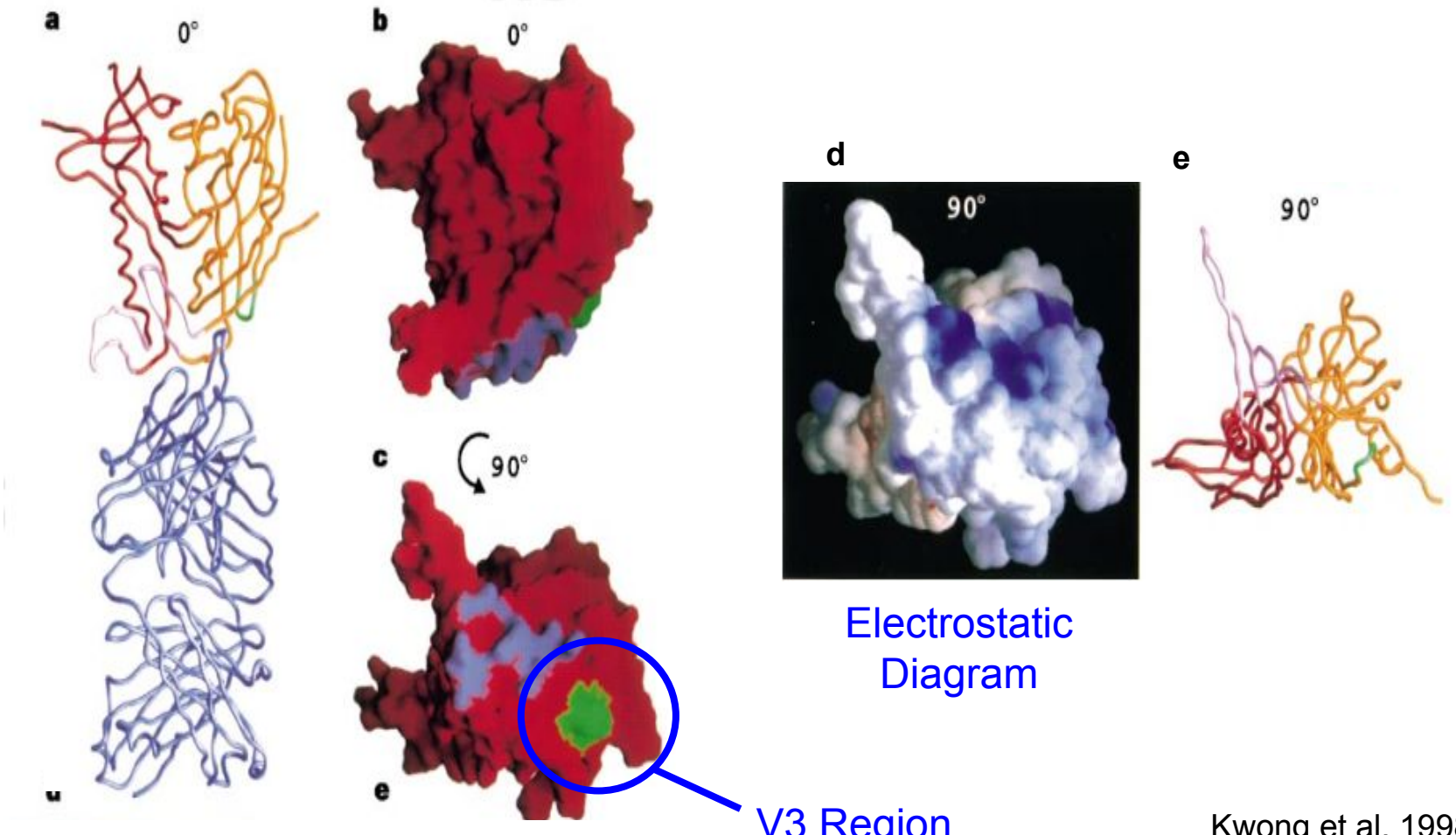
Kwong et al. 1998

CD4 Residues Phe43 and Arg59 Come in Direct Contact With the gp120



Kwong et al. 1998

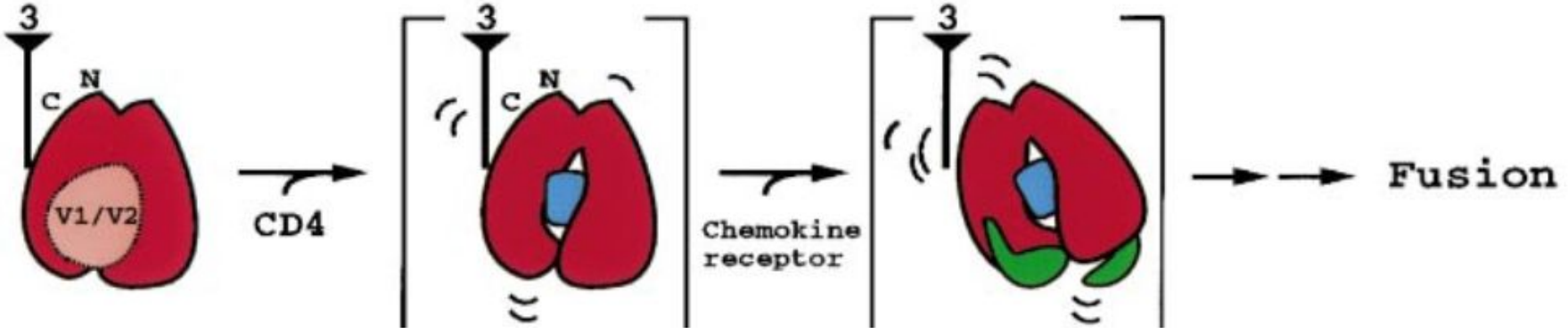
The 17b Antibody Binds with CD4i NAb and gp120, but the Interface Between the Proteins is Relatively Small



Kwong et al. 1998

A Series of Conformational Changes are Induced Through gp120-CD4 Binding, and Chemokine Receptor Binding

- **Structural analysis clarified details of mechanisms that lead to fusion:**
  1. Conformational change occurs when CD4 binds
     a. Inner/outer domain shift-Phe43 cavity forms
     b. Alters the orientation of the N and C termini-priming gp120 core
  2. Chemokine binds to V3 loop
     a. Orientational shift occurs
  3. Further changes are triggered, ultimately leading to fusion



Kwong et al. 1998

Summary

- **HIV-1 infection of host cells involves a primary receptor binding, co-receptor binding, and subsequent cell fusion.**

- **Understanding HIV-1 structures is important in explaining function and discovering treatments.**

- **Kwong et al. (1998) studied the structure and function of a HIV-1 ternary complexe containing gp120, CD4, and a neutralizing antibody.**

- **They modeled several structures of the gp120/CD4/NAb complex and determined how they aid in immune evasion and host cell infection.**

- **Future studies should analyze the structures of other stages of HIV-1 infection in order to better understand viral mechanisms.**

Acknowledgments

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LMU Department of Biology

References

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