

CHARACTERIZING THE RETROVIRAL ENVELOPE GLYCOPROTEIN MEMBRANE  
PROXIMAL EXTERNAL REGION AND MEMBRANE-SPANNING DOMAINS FOR THEIR  
ROLES IN HELICAL ALIGNMENT, FUSOGENICITY, AND INCORPORATION INTO  
VIRAL PARTICLES

Daniel Salamango

Dr. Marc Johnson, Dissertation Supervisor

ABSTRACT

Retroviruses readily form pseudotyped particles with a diverse panel of viral glycoproteins from similar and unrelated families. This phenomenon has been exploited by researchers from various fields for manipulation of retroviral vectors to target specific cell types. One limitation, however, is that very little is known about the pseudotyping mechanism. If we can gain insight into the molecular mechanism of this process, then potentially non-viral surface proteins could be engineered to incorporate into viral particles. This could greatly broaden the range of cell types that could be specifically targeted by lentiviral gene delivery vectors. My work has shown that the MSD of MLV Env has critical protein components necessary for fusogenicity and that the MPER and MSD both contribute to MLV Env incorporation into viral particles. Additionally, my work provided insight into the ability for the viral Env protein to accomplish viral-to-cell membrane fusion. I identified four hydroxyl-containing residues at the C-terminus of the MPER and N-terminus of the MSD that are critical for Env fusogenicity. Further study revealed that these residues may be part of a SxxxTTxxS motif previously observed to influence oligomerization of membrane helices. Interestingly, other gamma-retroviral glycoproteins such as FLV and GaLV Env also have this serine/threonine clustering. The same motif can also be found in VSV-G and in many different strains of the influenza virus, both A and B. It is plausible that this motif has an evolutionary advantage to aid in regulation of fusogenic activity.