DRAFT Questions for October 25:
General Questions on Lentivirus Vectors

1. What safety data should be available prior to initial use of HIV-based lentivirus vectors in phase 1 clinical trials? Please consider the following:
    a) Replication-competent lentivirus (RCL)
    b) Recombination between vector and wild-type HIV
    c) Mobilization of vector by wild-type HIV

2. What should be the appropriate species for *in vivo*, preclinical safety and toxicology evaluation of lentivirus vectors? Please consider the following:
    a) Wild-type HIV-1 does not infect monocytes, lymphocytes, or other target cells in rodents nor in cynomologous or rhesus macaques and will only poorly infect $CD4^+$ T lymphocytes from chimpanzees, so mobilization studies will be complicated
    b) Lentivirus vectors pseudotyped with different envelopes (i.e. VSV-G, rabies envelope, flaviviruses) may have expanded cell tropisms, but the infection may be limited (for example, mouse cells have multiple blocks to HIV replication in addition to receptor-mediated).

3. Given the limitations of the available animal models for study of vector safety and mobilization, please comment on whether in vitro assays are sufficient to address the safety issues of recombination, RCL generation, and rescue and/or mobilization of lentiviral vectors, assuming such assays were accompanied by limited safety data from *in vivo* preclinical proof-of-concept studies?