Abstract Conserved epitopes targeted by broadly neutralizing antibodies provide starting points for reverse engineering vaccines against antigenically variable pathogens such as HIV or influenza. However, there has been considerable uncertainty about whether the strategy of vaccine reverse engineering can produce neutralizing antibodies for any virus, and even greater uncertainty on whether such methods can induce broadly neutralizing antibodies against HIV or influenza. The first part of this talk will describe a study that demonstrates proof of principal for structure-based, epitope-focused vaccine design, employing an epitope from respiratory syncytial virus. The second part of the talk will review our efforts employing computational and in vitro screening approaches to devise immunogens and regimens that focus immune responses to particular HIV structural epitopes, activate appropriate germline B cells and select appropriate somatic mutation, with the goal of eliciting broadly neutralizing antibodies of certain specificities.