APPLICATIONS OF HIGH-THROUGHPUT SINGLE B-CELL SEQUENCING TO ACCELERATE RATIONAL VACCINE DESIGN

Brandon DeKosky, Vaccine Research Center, NIAID, Bethesda, MD
brandon.dekosky@nih.gov
Erica Normandin, Vaccine Research Center, NIAID, Bethesda, MD
Cheng Cheng, Vaccine Research Center, NIAID, Bethesda, MD
Hongying Duan, Vaccine Research Center, NIAID, Bethesda, MD
Xuejun Chen, Vaccine Research Center, NIAID, Bethesda, MD
Maryam Mukhamedova, Vaccine Research Center, NIAID, Bethesda, MD
Sarah Andrews, Vaccine Research Center, NIAID, Bethesda, MD
Amy Ransier, Vaccine Research Center, NIAID, Bethesda, MD
Sam Darko, Vaccine Research Center, NIAID, Bethesda, MD
Hugh Welles, Vaccine Research Center, NIAID, Bethesda, MD
Mario Roederer, Vaccine Research Center, NIAID, Bethesda, MD
Peter Kwong, Vaccine Research Center, NIAID, Bethesda, MD
Danny Douek, Vaccine Research Center, NIAID, Bethesda, MD
Adrian McDermott, Vaccine Research Center, NIAID, Bethesda, MD
Nancy Sullivan, Vaccine Research Center, NIAID, Bethesda, MD
1. John Mascola, Vaccine Research Center, NIAID, Bethesda, MD

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Understanding the antibody repertoire response to vaccination is critical for the rational design and evaluation of experimental vaccines. Immune receptors comprise two chains encoded by separate mRNA strands and thus conventional NextGen sequencing fails to identify the native pairings encoded by individual lymphocytes. To overcome this limitation, we are applying recent technical advances in high-throughput sequencing of complete antibodies (i.e., paired heavy and light chain sequencing) to generate a quantitative understanding of experimental vaccine performance and to accelerate vaccine design. We apply repertoire-based metrics of vaccine-elicited antibodies to evaluate and select promising candidate immunogens for inducing HIV-1 Envelope-specific VRC01-class antibodies. The VRC01 class of broadly neutralizing antibodies have been observed in multiple individuals and targets the HIV CD4 binding site via a common recognition motif that requires specific features in both heavy and light chains (e.g., VH1-2 heavy chain V-gene and a short, $\leq$5 amino acid light chain CDR3). We are using paired heavy and light chain sequencing to quantify the performance of various candidate HIV immunogens for inducing VRC01-class broadly neutralizing HIV antibodies in transgenic mouse models. We are also elucidating the ontogeny of antibodies in vaccinated and naturally infected human subjects and animal models via interrogation of paired heavy and light chain antibody sequences and antibody synthesis/testing of promising clones, including experimental influenza vaccine trials and a Phase I Ebola vaccine trial. These next-generation immunoanalytic approaches are providing detailed molecular feedback regarding experimental vaccine performance to accelerate vaccine design efforts against pathogens of major public health importance.