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Areas of Interest

1. **HIV entry and resistance to neutralizing antibodies:**
   My long-term commitment to research in virology and viral immunology began with graduate work to define virus-host interactions for HIV, where my studies of virus entry defined molecular structural rearrangements required for HIV binding to its co-receptor, and led to my discovery that unique structures of primary HIV-1 isolates rendered them able to use a novel second receptor, CCR5, and to resist the same neutralizing antibodies that readily blocked lab-adapted HIV-1 isolates.

2. **Filovirus vaccines and immune mechanism**
   Incorporating my interest and experience in virus entry and host interactions into my work on filoviruses, I began with the question of why decades of research failed to yield a vaccine that could protect primates from Ebola infection. By focusing first on Ebola virus entry and pathogenesis, I hypothesized successfully that a primate Ebola vaccine would need to induce both antibodies and T-cells. Following studies to optimize induction of this balanceimmune response, I discovered the first vaccine to protect primates from Ebola virus infection (*Nature 408:605-9; Nature. 424:681-4*), defined CD8 T-cells as the primary mechanism of protection (*Nat Med. 17:1128-3*), and co-led, with Dr. Julie Ledgerwood, the first Ebola vaccine clinical trials in both the U.S. (*Clin Vaccine Immunol. 13:1267-77; N. Engl. J Med. 373:775-776*) and Africa (*Lancet 385:1545- 54*). . This was followed by my discovery of a single shot vaccine that provided more immediate protection, making it a very practical vaccine that could be used in the face of an acute Ebola epidemic. As a result, this vaccination schedule is now standard in the field of Ebola vaccine research, where one of the lead Ebola vaccine candidates, ChAd3-EBOV, was deployed in a Phase III clinical trial during the West Africa 2013-2016 outbreak, and multiple international Phase IIb trials for which my laboratory conducted the immune assessments needed to define an immune correlate of protection. Another vaccine discovered in my lab, ChAd3-SUDV was deployed to Uganda during the outbreak of 2022.

3. **Filovirus glycoprotein mediated pathogenicity, virus entry and antibody vulnerabilities:**
   My research program leverages cross-cutting data from vaccine, virus entry and virus-antibody interactions. We showed that the Ebola envelope glycoptrotein, GP is a key determinant of pathogenicity, mediating specific cytopathic effects and vascular leakage that is characteristic of filovirus infection of primates. We also defined elements of the virus entry pathway, including receptor binding and GP cleavage by intracellular cathepsins that were critical points of vulnerability for neutralizing antibodies, an unanticipated finding given that both events occur only after the virus has been internalized into the cell endosomes via micropinocytosis. We identified an Ebola antibody mAb114 that we derived from a human Ebola survivor that completely rescues Ebola-infected primates, even when given as a monotherapy several days after their Ebola exposure. Studies with the antibody demonstrated that the most potent mechanism of antibody protection is through high affinity, low pH-stable binding that blocks a critical Ebola interaction with its intracellular receptor, Neimann-Pick C1. We brought this mAb through Phase I clinical trials (*Lancet. 393:889-898*) and it has since been deployed in Africa as a potent therapeutic for Ebola patient treatment, resulting in FDA licensure as *Ebanga* by Ridgeback Biotherapeutics.

4. **Pandemic Preparedness:**
   My work on filovirus protective immunity that began in the late 1990s and for which we continued vaccine and therapeutic evaluation through Phase I trials, prepared the United States Government to respond to and contain three filovirus outbreaks. Through these experiences and our observed increasing frequency of filovirus outbreaks, it became clear to me that pathogen readiness (vaccines and therapeutics “on the shelf”) was needed to prevent future outbreaks, epidemics, and pandemics. Knowing

that there are far too many viruses to fully define immune mechanisms and vaccine approaches for each one, my colleague Barney Graham and I developed the Prototype Pathogen Approach to prepare for potential pandemics and published our approach in 2018, two years before SARS-CoV-2 emerged. I am currently developing vaccines and therapeutics for MPOX, Nipah/Hendra, SARS-CoV-2, Marburg and Sudan viruses, with the aim of applying lessons learned on their immune mechanisms to other prototype pathogens and moving each through Phase I trials to enable accelerated development and emergency use in future potential outbreaks.

5. **SARS-CoV-2:**
We at the NIAID NIH Vaccine Research Center were well positioned as a PI group to respond to the COVID-19 outbreak in part due to our bench to bedside model for research, but also because Barney Graham and Jason McLellan had previously solved the structures for respiratory virus glycoproteins with structural similarity to SARS-CoV-2. With Moderna, we quickly developed genetic constructs for mRNA vaccine delivery, and conducted preclinical evaluation in nonhuman primates that demonstrated potent vaccine efficacy. At the same time, we isolated hundreds of monoclonal antibodies using B-cells from the index patient from which the WA-1 virus was derived. The first potently neutralizing mAb, LY-CoV1404 (bebtelovimab), was developed by Eli Lilly and remained in broad clinical usage until late Omicron lineages for which it lost potency. Subsequently, we embarked on efforts make multispecific antibodies that retain potency across all SARS-CoV-2 variants.