Lisa Lindesmith, Clin Microbiol 2016, 5:5(Suppl)
http://dx.doi.org/10.4172/2327-5073.C1.024

6th Clinical Microbiology Conference

Norovirus diversity and immune-driven evolution: Mechanisms of protection and implications for vaccine design

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*Norovirus*es (NoVs) are the leading cause of human acute gastroenteritis. Strains within the GII.4 genotype drive pandemic levels of infection every 2-3 years. Each pandemic strain correlates with evolution in the major capsid protein and emergence of a GII.4 strain with distinct antigenic and ligand binding properties. GII.4 strain emergence and extensive antigenic heterogeneity among the >40 additional NoV genotypes are primary obstacles to development of an efficacious vaccine. Multivalent virus-like particle (VLP) vaccination shows promise for overcoming these challenges. Volunteers vaccinated simultaneously with GI.1 and GII.4C VLPs generated broad cross-genotype blockade antibody responses, a surrogate measurement for protective immunity. Importantly, breadth of blockade antibody response extended to novel GII.4 VLPs that had not circulated prior to sample collection, indicating that vaccination may provide protection from emergent strains. The breadth and uniformity of the blockade antibody response across antigenically diverse GII.4 strains suggests that immunization primarily activated a memory antibody response to multiple GII.4 strains. Antigenic cartography and epitope-specific blockade-of-binding assays support this finding. These results are in contrast to the observed strain-specific secondary antibody response to the GI.1 vaccine component and identify pre-exposure history, mediated by host genetics, as a key determinant to NoV vaccine response.

Biography

Lisa Lindesmith is a Research Specialist collaborating with Dr. Ralph Baric since 1999 to study the molecular mechanisms regulating *Norovirus* evolution, susceptibility and protective immunity. Her major contributions include identification of FUT2 (histoblood group antigen expression) as a major *Norovirus* susceptibility allele, demonstration that GII.4 *norovirus*es are evolving by epochal evolution in response to human herd immunity, first to map neutralizing blockade epitopes elucidating the molecular mechanisms which allow GII.4 *Norovirus* escape from herd immunity and first to identify strategies to increase the breadth of blockade immune responses by multivalent vaccination in mice and humans.

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