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Title of Presentation: Human fecal transplantation into germ-free mice as a model to assess the *in vivo* impact of intestinal microbiota on early life immunity.

Abstract

Infancy is a period of greater susceptibility to infection, due in part to the suboptimal immune system. We focus on developing immunization strategies to help reduce the global burden of infant death from infectious disease. However, infants in developing nations are not only more susceptible to infection than their first-world counterparts, but respond differently to current vaccines. In our attempt to identify the underlying mechanisms for this difference between infants from the developed vs. developing world we wished to characterize how the innate immune system differs by measuring innate cytokine responses to Toll-like receptor (TLR) stimulation.

Surprisingly, infants from South Africa (SAF) under-responded to most TLR stimulants compared to Canadian (CAD) infants and this occurred irrespective of ethnic background, which suggests modulation by environmental exposure. The gut microbial ecosystem, or microbiota, has gained increasing prominence as a key environmental modulator of immune ontogeny. We hypothesized that an aberrant microbiota could lead to altered host immunity and increased risk for infection in early life. To address our hypothesis, we assessed the fecal microbiota of SAF and CAD infants by high-throughput sequencing the bacterial 16S rRNA gene. Furthermore, to begin probing for cause-and-effect relationships, we utilized a germ-free (GF) mouse model of adoptive human fecal transplantation to assess the effects of gut microbiota on intestinal homeostasis and innate immune phenotype.

The gut microbiota was distinct between cohorts with SAF dominated by *Prevotella* and CAD but *Bacteroides* at the genus level. Our animal data suggest that the SAF microbiota was associated with significantly increased gut permeability and villous blunting consistent with enteropathy. While proinflammatory cytokine production remained unchanged in the spleen, SAF microbiota was associated with a decreased IL-10, IL-6, and IFN-γ response to TLR agonists. Similar trends were seen in the children that the fecal samples originated from. . This suggests that cause-effect relationships can be dissected using this model. In future studies we will utilize this model to assess susceptibility to infection and screen for effective therapeutic interventions.