Gut Microbiome Initiative

The Global Health Center, headed by William Powderly, MD, is working with the Center Gut Microbiome and Nutrition Research, directed by Jeffrey Gordon, MD, and a multidisciplinary team of Washington University faculty and trainees in an initiative designed to address a range of scientific, regulatory, ethical, social, cultural, and policy considerations that underpin the development of next generation nutribiotics for childhood undernutrition.

The gut is the home of our largest microbial community harboring tens of trillions of microorganisms, belonging to all three domains of life on Earth, and their viruses. Recent advances in next-generation sequencing and the use of gnotobiotic animal models have shed new light on the importance of normal gut microbial community development to healthy growth. Work in the Gordon lab on childhood undernutrition is supported by the Bill & Melinda Gates Foundation (BMGF) through the Breast Milk, Gut Microbiome and Immunity (BMMI) Project; this project includes a long-standing collaboration with Dr. Tahmeed Ahmed and his colleagues at the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).

As part of this collaboration, we applied a machine learning approach (Random Forests) to bacterial 16S rRNA datasets generated from fecal samples, collected each month, from birth through the first 5 years of postnatal life from infants/children with healthy growth phenotypes (as defined by serial anthropometry). The results yielded a group of the most age-discriminatory bacterial strains; together these strains serve as a microbial signature for defining a program of normal gut microbiota development (maturation) that shared across biologically unrelated healthy infants/children. This program is largely completed during the first 3 years of life (Subramanian et al., 2014). By extending these studies to birth cohorts from five other countries where the burden of undernutrition is great (Brazil, India, Malawi, Peru, South Africa), we have determined that many of the bacterial strains that define this program of gut microbiota development/maturation are shared across healthy children living in very distinct geographic and cultural settings.

These Random Forests-derived models can be used to define the state of maturation of a child's gut microbiota sample relative to his/her chronologic age. We have used a metric derived from this approach ['microbiota for age Z-score' (the degree of deviation of the state of development (age) of a given individual's microbiota from that of a reference cohort of chronologically-matched healthy children)] to show that gut microbial community assembly is perturbed in children with undernutrition, resulting in persistent microbiota immaturity (i.e. the microbiota has a configuration that is 'younger' than that seen in individuals with healthy growth phenotypes) (Subramanian et al., 2014; Blanton et al., 2016a). Importantly, this immaturity is not rescued by current nutritional interventions: in other words, these children have a persistent developmental abnormality affecting their gut microbial 'organ'.

Using recently weaned germ-free mice fed macro-/micronutrient deficient diets representative of those consumed by the human donors, we have demonstrated that transplantation of immature gut microbiota from undernourished Malawian infants/children results in significantly reduced growth in recipient animals compared to mice receiving microbiota from chronologically age-matched donors with healthy growth phenotypes (Blanton et al., 2016a). These studies also revealed that a number of the age-discriminatory taxa used to define microbiota maturity are more than just biomarkers but are also effectors of healthy growth. Addition of a subset of these growth-discriminatory strains to a stunted, underweight child's microbiota prior to its transplantation to young germ-free mice ameliorated the growth faltering and metabolic abnormalities that an untreated microbiota could transmit. These findings provide preclinical evidence for a causal relationship between microbiota immaturity and the pathogenesis of childhood undernutrition and its lingering sequelae; they also reveal bacterial taxa that are potential therapeutic targets for food-based interventions designed to promote healthy growth.

We hypothesize that durable repair of microbiota immaturity will yield improved clinical outcomes in children with already manifest undernutrition, and that preventing the arrest of normal microbiota maturation in children before the onset of growth faltering will improve developmental outcomes. The microbiota therefore provides a target for new food and microbial approaches for disease treatment and ultimately prevention that are derived from a discovery platform involving gnotobiotic animals colonized with human gut communities.

A central hypothesis that is being tested in the BMMI Project is that specific culturally acceptable and locally-available complementary food ingredients consumed by children during the weaning period have the capacity to promote adequate representation of age/growth- discriminatory strains, and that supplementation of diets with these ingredients (i.e. Microbiota-Directed Complementary Foods; 'MDCFs') will repair microbiota immaturity and associated growth /metabolic deficits in undernourished children. We used gnotobiotic animals harboring human gut microbial community members to identify lead MDCF prototypes.

The identification of foods that promote healthy growth and wellness by promoting healthy development of the microbiota raises a number of issues that have important implications for society. This initiative between The Global Health Center, the Center for Gut Microbiome and Nutrition Research and icddr,b will seek to address not only the key scientific and commercial issues, but critically, a range of regulatory, ethical, social, cultural, and policy/governance considerations that must be addressed to enable successful development and implementation of MDCFs in vulnerable populations (Blanton et al., 2016b).

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