Rebuilding the Infant Gut Microbiome: Insights from Ecology and Evolution.

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The scientific community has been increasingly intrigued by the epidemiologic descriptions of intestinal microbiomes of individuals with metabolic, autoimmune and inflammatory diseases. However, the mechanisms behind many of these observations have not explained, resulting in the absence of clear intervention strategies. Ongoing research at UC Davis has made a number of important discoveries linking the evolution of lactation and the mammalian gut microbiome. These breakthroughs are revealing the mechanisms for controlling this microbial ecosystem and its importance to the development, disease resistance, and long term health outcomes of milk-fed neonates. A central paradigm in the control of this ecosystem is the explicit gut microbe-glycan interaction, driven by dietary components and shown to have a profound effect on the gut microbial ecology and metabolism. Thus, dietary glycans have the potential to encourage specific taxa that benefit the host, or to facilitate the expansion of dysbiotic taxa and damage the host.

Previous work at UC Davis and elsewhere has highlighted the importance of key complex milk glycan substrates in cross-feeding intestinal bacterial populations, resulting in gut dysbiosis, or outright infection. By applying an understanding of the ecological forces governing the gut microbiome, and how evolutionary pressures have shaped this relationship, we have developed solutions that incorporate these concepts and deployed them in a variety of clinical settings. In doing so, we found that we are able to formulate stable replacement microbial communities to reduce the abundance of taxa associated with dysbiosis in neonates. Applying this to animal models, we found that these communities were sufficient to dramatically alter health outcomes even in a real life outbreak scenario. In humans, we applied this same strategy in a 'restoration ecology' approach to restore a keystone species, in a controlled clinical trial of *Bifidobacterium longum* subspecies *infantis* in human infants and found that stable, specific associations between this subspecies and the milk-fed human infant had a profound effect on both the gut microbiome and the host. Together, these findings fundamentally alter the paradigm of gut microbiome therapeutics and offer a sound, mechanistic pathway toward gut microbiome reconstruction and alleviation of disease in both humans and animals, starting in milk-fed neonates.