Systematic development of pro- and pre-biotic treatments for atopic dermatitis.

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The underlying pathology of atopic dermatitis (AD) includes impaired skin barrier function, susceptibility to *Staphylococcus aureus* skin infection, immune dysregulation, and cutaneous dysbiosis. This dysbiosis of the skin (and gut) microbiota is increasingly implicated in the pathogenesis of AD. We previously reported first-in-human safety and clinical activity results from topical application of the commensal skin bacterium *Roseomonas mucosa* for the treatment of AD in 10 adults and 20 children in the open label phase of development (BACTERiAD I/IIa). Twice weekly *R. mucosa* treatment was associated with amelioration of disease severity, improvement in epithelial barrier function, reduced *S. aureus* burden on the skin, and a reduction in topical steroid requirements without severe adverse events. Importantly, skin improvements and colonization by *R. mucosa* persisted for up to 8 months after cessation of treatment – suggesting the potential for long-term benefit resulting from short-term therapy. Although the repeat-measures analysis is embargoed by the private sector licensee, reported group-wise assessments of the placebo-controlled Phase IIb demonstrated positive statistical trends for improvement in disease measures by *R. mucosa* treatment.

In addition to the probiotic approach, we recognize that patients and families struggling with AD have documented concerns for a contributory role of skin care products in disease pathology. Nearly all the skin microbiome studies to date have asked participants to avoid topical products (such as soaps or select medications) for the preceding days to weeks prior to sample collection. Thus, given the established role of the microbiome in AD, the interactions between topical exposures, dysbiosis and AD remains underrepresented in the academic literature. To address this knowledge gap, we expanded our previous evaluations to test the toxicological effects of a broader range of common chemicals, AD treatment lotions, creams and ointments using both health- and AD-associated strains of *R. mucosa* and *Staphylococcus* spp. Use of in vitro culture techniques and mouse models were deployed to identify chemicals with dysbiotic or pre-biotic potential. These revealed that numerous chemicals possessed antibiotic properties, including many not marketed as anti-microbials. Through targeted combination of potentially beneficial chemicals, we identified combinations which promoted the growth of health-associated isolates over disease-associated strains in bacterial culture and enhanced microbe-specific outcomes in an established mouse model of AD; the most promising of which was the combination of citral and colophonium (often sold as lemon myrtle oil and pine tar respectively). Using dermatologic patch testing, similar results were shown in a proof-of-concept study in healthy volunteers to assess global microbiome shifts after exposure.

Therefore, our probiotic approach offers the potential to create clinical benefit while colonizing the patients to provide efficacy without the need for continued treatment applications or financial burden. Meanwhile our pre-biotic results could offer a systematic, multiplex approach to identify which products carry dysbiotic potential and thus may guide

formulation of new topicals to benefit patients with AD. Overall, these approaches highlight unique aspects of AD treatments that opt to target the microbiome that must be considered if this revolutionary approach is to succeed. First, isolate-level identification is essential to properly assess clinical impacts of probiotic treatments. Second, global microbiome assessments beyond simple *S. aureus* reduction must be used when assessing treatment impacts on the microbiome. Third, the ability to colonize patients likely invalidates the standard clinical trial practice of imputation; since protracted exposure to treatment may be possible even for study participants that withdrew early, subsequent outcomes cannot be assumed in ways that may be apt for drugs with short half-lives. Finally, rather than only considering the active treatment phase, efficacy assessments should occur after treatment washout periods to evaluate the potential for colonization-related disease modification.