The human microbiome as source and target for new antibacterial compounds

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The majority of bacterial infections including those caused by antibiotic-resistant ESKAPE pathogens arise from microorganisms that use human microbiomes as their major habitat. However, these endogenous pathogens do not belong to the core taxa of human microbiomes and they are absent from many humans. Mounting evidence indicates that it is the presence of beneficial commensals that precludes colonization by ESKAPE pathogens. Our laboratories investigate, which commensal bacteria contribute to exclusion of the major bacterial pathogen *Staphylococcus aureus* from the nasal microbiome in 70% of the human population. We found that a large percentage of nasal commensal *Staphylococcus* species produces antimicrobial compounds with the capacity to eliminate *S. aureus*. Many of these compounds are founding members of new classes of natural products with unusual antimicrobial modes of action. The cyclic fibupetide lugdunin, produced by *Staphylococcus lugdunensis*, acts as an ionophore and does not provoke notable resistance development. The complex peptide-polyene epifadin is produced by certain strains of *Staphylococcus epidermidis*. It has broad antibacterial activity but a very short half-life, probably to limit collateral damage of microbiome integrity. Further novel compound classes from human microbiomes are currently under investigation. Funding from Tübingen's Cluster of Excellence "Controlling Microbes to Fight Infections (CMFI)" and from the German Center for Infection Research (DZIF) allow the preclinical and clinical development of new microbiome-derived probiotic bacterial strains or their antimicrobial compounds to be used for elimination of *S. aureus* or other ESKAPE pathogens from the microbiomes of at-risk patients.

Zipperer et al (2016) *Nature* 10:539; Heilbronner et al (2021) *Nat Rev Microbiol* 19:726; Torres-Salazar et al (2024) *Nat Microbiol* 9:200.