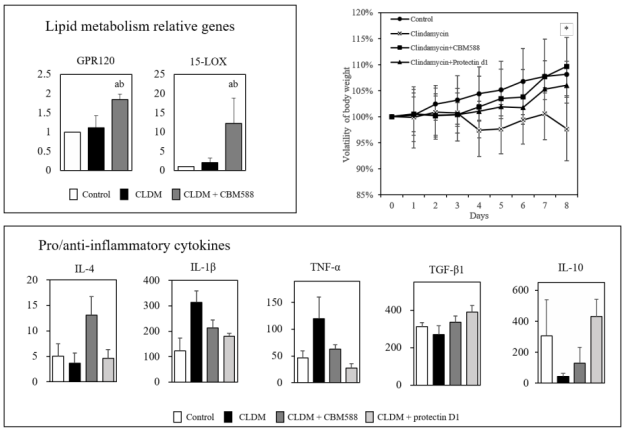
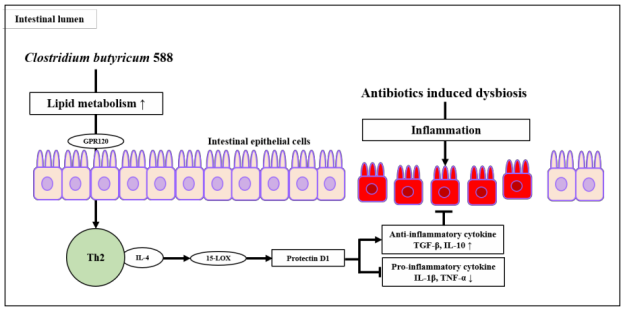
Lipid metabolism relative genes, pro/anti-inflammatory cytokines and body weight.



Conclusion. Our data suggested that CBM 588 stimulated PUFAs metabolism in the intestinal tract, and that PUFAs were signaled to Th2 cells as a ligand of GPR120. It was speculated that the stimulated Th2 cells produced IL4 and activated 15-LOX, resulting in the induction of protectin D1. Also, it became clear that protectin D1 induced anti-inflammatory cytokines in controlling antibiotic-induced gut inflammation. We provide as a new insight that lipid metabolism induction for the treatment of gut inflammatory diseases with CBM 588.

Anti-inflammatory pathway of protectin D1 induced by CBM 588.



Disclosures. **Hiroshige Mikamo, M.D, Ph.D**, **Astellas Pharma Inc.** (Grant/Research Support, Speaker's Bureau)**MSD Japan** (Grant/Research Support, Speaker's Bureau)**Pfizer Japan Inc.** (Grant/Research Support)**Sumitomo Dainippon Pharma Co., Ltd** (Grant/Research Support, Speaker's Bureau)

1206. Association of Aging, Frailty and Place of Residence with Skin, Oral and Gut Microbiome Characteristics and Pathogenicity Reservoirs

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Session: P-54. Microbiome in Health and Disease

Background. Despite their elevated risk for morbidity and mortality from infections, the microbiota of older adults remain understudied. While colonization resistance from resident microflora is a promising means to prevent infections, little is known about pathogenicity reservoirs and colonization resistance in this vulnerable population. Here we study the skin, oral, and gut microbiome dynamics of older adults in both community and Skilled Nursing Facility (SNF) settings, investigating relationships between age, frailty, environment, microbiota, and pathogenicity reservoirs.

Methods. We conducted a longitudinal metagenome survey of 47 adults age 65+ years of age; 22 residents of 3 different SNFs and 25 community dwelling individuals. We performed metagenomic whole genome shotgun sequencing on stool, oral, and skin samples from 8 sites, 1421 total. To correlate clinical and behavioral variables, we measured frailty, collected medical records, and interviewed participants on diet and lifestyle. We also draw comparisons with previous younger cohorts.

Results.
- Compared to younger adults, the skin microbiota of older adults was characterized by
  - High heterogeneity
  - Decreased stability over time, suggesting increased susceptibility to colonization and pathogenicity
  - Compositional differences including significantly lower levels of *Cutibacterium acnes,* with reciprocal increases in Staphylococci, Corynebacteria, and Malassezia
- In older adults, Frailty (Rockwood) was found to have linear correlation with relative abundance of species relevant to infection risk including *acnes,* staphylococci, streptococci, *E. coli, Akkermansia mucinophila,* and *Enterococcus faecalis*.
- The skin, oral, and gut microbiota of SNF residents had substantially elevated virulence factor and antibiotic resistance genes.

Conclusion. To the best of our knowledge, this is largest report to date of the skin metagenome in older adults. We demonstrate distinct and significant differences between cohorts with clinically relevant implications. We believe these results may inform infection control and prevention by increasing our understanding of colonization resistance and pathogenicity reservoirs, as well as advance our knowledge of the relationship between aging, the microbiome, and infections.

Disclosures. **All Authors**: No reported disclosures

1207. Combining standard bacterial vaginosis treatment with cystine uptake inhibitors to block growth of Lactobacillus iners is a potential a target for shifting the cervicovaginal microbiota towards health-associated Lactobacillus crispatus-dominant communities

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Session: P-54. Microbiome in Health and Disease

Background. Cervicovaginal microbiota domination by *Lactobacillus crispatus* is associated with beneficial health outcomes, whereas *L. iners* dominance has more adverse associations. However bacterial vaginosis (BV) treatment with metronidazole (MTZ) typically leads to domination by *L. iners* rather than *L. crispatus*. *L. iners* differs from other lactobacilli by its inability to grow in MRS media. We hypothesized that exploring this growth difference would identify targets for selective *L. iners* inhibition.

Methods. Bacteria were grown anaerobically. Nutrient uptake and metabolism were assessed using UPLC-MS/MS and isotopically labeled substrates. Bacterial genome annotation employed Prodigal, Roary, and EggNOG. Competition experiments with mock mixed communities were analyzed by 16S rRNA gene sequencing. We confirmed result generalizability using a diverse collection of South African and North American strains and genomes.

Results. Supplementing MRS broth with L-cysteine (Cys) or L-cystine permitted robust *L. iners* growth, while *L. crispatus* grew without Cys supplementation. Despite their different growth requirements, neither species could synthesize Cys via canonical pathways. Adding the cystine uptake inhibitors S-methyl-L-cysteine (SMC, Fig 1) or seleno-DL-cystine (SDLC) blocked growth of *L. iners* but not other lactobacilli, suggesting *L. iners* lacks mechanisms other lactobacilli use to exploit complex exogenous Cys sources. Notably, cydABCD, an operon with Cys/glutathione transport and redox homeostasis activities, is absent from *L. iners* but present in non-*iners Lactobacillus* species. Consistent with possible roles for cydABCD in explaining the observed phenotypes, (1) *L. iners* failed to take up exogenous glutathione and (2) supplementing MRS with reducing agents permitted *L. iners* growth, which could be blocked by SMC or SDLC. In growth competitions testing *L. iners* and *L. crispatus* within mock BV-like communities, SMC plus MTZ outperformed MTZ alone in promoting *L. crispatus* dominance (Figs 2&3).

Figure 1: S-methyl-L-cysteine (SMC) selectively blocks growth of L. iners but not other cervicovaginal Lactobacillus species in cysteine-supplemented MRS broth. Growth was measured by optical density and inhibition calculated relative to Cys-supplemented no-inhibitor control during exponential growth. Values displayed are median (+/- maximum/minimum) for 3 replicates from a single experiment. In all panels, representative data are shown from 1 of >=2 independent experiments for each bacterial strain and media condition. Results are representative of multiple strains for L. iners (n = 16), L. crispatus (n = 7), and L. jensenii (n = 2).

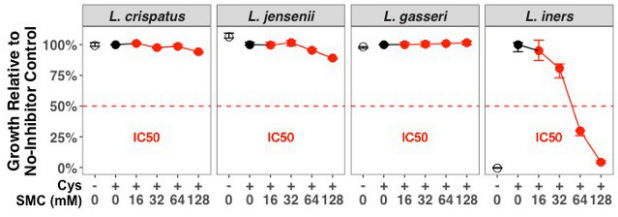


Figure 2: Relative abundance of L. crispatus, L. iners, or various BV-associated bacteria in mock bacterial communities grown in rich, non-selective media with or without metronidazole (MTZ) and/or SMC. Relative abundance was determined by bacterial 16S rRNA gene sequencing. Data are shown for three representative mock communities with 5 replicates per media condition.

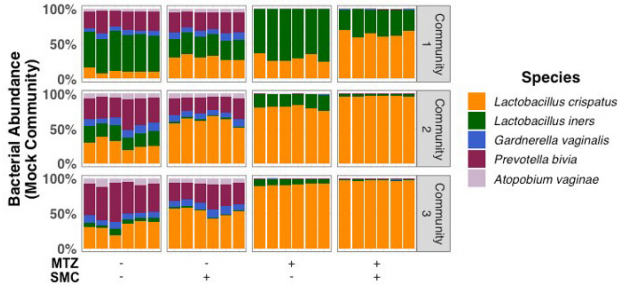
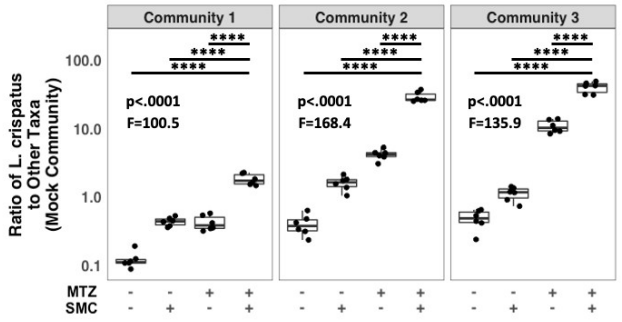


Figure 3: Ratio of L. crispatus to other species in the mock bacterial communities depicted in Figure 2. Statistical significance determined via 1-way ANOVA of log10-transformed ratios with post-hoc Tukey test; selected pairwise comparisons are shown (***, p < 0.001).



Conclusion. *L. iners* has unique requirements for exogenous cysteine/cystine or a reduced environment for growth. Targeting cystine uptake to inhibit *L. iners* is a potential strategy for shifting cervicovaginal microbiota towards *L. crispatus*-dominant communities.

Disclosures. **Douglas S. Kwon, MD, PhD**, **Day Zero Diagnostics** (Consultant, Shareholder, Other Financial or Material Support, co-founder)

1208. Development of a Novel Synthetic Glycan to Prevent Bacterial Infections and Ameliorate Respiratory Viral Infections

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Session: P-54. Microbiome in Health and Disease

Background. The prevention and treatment of bacterial infections is a human health challenge. A disadvantage of antibiotics is that they often kill beneficial commensal, bacteria in addition to, pathogenic bacteria. Indiscriminate killing disrupts the homeostasis between commensal bacteria and the host gut epithelium allowing colonization of the gut by pathogenic bacteria and increases susceptibility to infections. This research was done to develop a non-antibiotic modality to prevent bacterial infections by growing, rather than killing, commensal bacteria in the gut. Gut commensal bacteria grown on carbohydrates produce short-chain fatty acids (SCFAs) that support gut homeostasis maintenance and promote resistance to bacterial colonization. SCFAs have direct and indirect effects on the gut and lung mucosal immune system. They have also been linked to respiratory viral infection reduction and shown to influence macrophage function to mitigate pro-inflammatory neutrophil-mediated tissue damage.

Methods. A library of over 1,500 synthetic proprietary glycans, termed Microbiome Metabolic Therapies (MMT™), was synthesized using different chemical and enzymatic approaches. An *ex vivo* platform using fecal bacterial communities from human subjects was devised to screen MMTs for their abilities to deplete pathogenic bacteria, and modulate multiple aspects of bacterial metabolism.

Results. KB109 was identified based on its ability to reduce the relative abundance of a diversity of pathogens including clinically relevant Gram-negative and Gram-positive bacteria in human fecal communities. KB109 also increased the relative abundance of prevalent commensal bacteria. Monoculture experiments demonstrated that KB109 promotes the growth of commensal bacteria, but not pathogens. *Ex vivo* screening revealed that KB109 consistently increased SFCA production across multiple fecal communities.

Conclusion. KB109 represents an appealing activity profile and offers an opportunity to prevent enteric and systemic bacterial infections by promoting gut homeostasis and colonization resistance, and ameliorating respiratory viral infections by stimulating immune homeostasis. KB109 is under evaluation in two COVID-19 clinical studies.

Disclosures. Jeffrey Meisner, PhD, Kaleido Biosciences (Employee, Shareholder) Jackson Lee, PhD, Kaleido Biosciences (Employee, Shareholder) Jonathan Lawrence, PhD, Kaleido Biosciences (Employee, Shareholder) Megan Roed, BA, Kaleido Biosciences (Employee, Shareholder) Johan van Hylckama Vlieg, PhD, Kaleido Biosciences (Employee, Shareholder)

1209. Impact of Respiratory Staphylococcus aureus Abundance on Risk for Ventilator-Associated Pneumonia During Long-Term Care

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Session: P-54. Microbiome in Health and Disease

Background. Patients admitted to long-term acute care hospital (LTACH) for ventilator weaning are at high risk for ventilator-associated pneumonia, which may contribute to adverse ventilator-associated events (VAE). *Staphylococcus aureus* (*Sa*) is a common cause of VAP. We sought to evaluate the impact of respiratory *Sa* colonization and bacterial community dominance on subsequent *Sa* VAP and VAE during long-term acute care.

Methods. We enrolled 83 subjects dependent on mechanical ventilation at LTACH admission, collected endotracheal aspirates, performed 16S rRNA gene sequencing (Illumina HiSeq) and bacterial community profiling (QIIME2). Statistical analysis was performed with R and Stan; mixed effects models were fit to relate the abundance of respiratory *Sa* on admission to clinically-diagnosed VAP and VAE.

Results. Of the 83 subjects, 8 were diagnosed with *Sa* pneumonia during the 14 days prior to LTACH admission ("Known *Sa*"), and 17 additional subjects received anti- *Sa* antibiotics within 48 hours of admission ("Suspected *Sa*"); 58 subjects had no known or suspected *Sa* ("Unknown *Sa*"). Among the Known *Sa* group, all 8 had *Sa* detectable by 16S sequencing, with elevated admission *Sa* proportional abundance (median 0.36; range 0.0013 - 1). Among the Suspected *Sa* group, only 7 had *Sa* detectable by 16S sequencing, with a wide range of admission *Sa* proportional abundance (median 0; range 0 - 0.96). 25 of 58 subjects in the Unknown *Sa* group also had detectable respiratory *Sa*, and a wide range of *Sa* proportional abundance at admission (median 0; range 0 - 0.93). Incident *Sa* VAP was observed within 30 days among 2 (25%) of the Known *Sa* subjects, 0 (0%) of the Suspected *Sa* subjects, and 3 (5.17%) of the Unknown *Sa* subjects. VAE was observed within 30 days among 0 (0%) of the Known *Sa* subjects, 3 (18%) of the Suspected *Sa* subjects, and 1 (1.7%) of the Unknown *Sa* subjects. Admission *Sa* abundance was positively associated with 30-day VAP risk in the Suspected *Sa* (type S error < 0.001) and Unknown *Sa* (type S error < 0.001) groups.

Conclusion. Among patients admitted to LTACH for weaning for mechanical ventilation, we observed a high prevalence of respiratory *Sa* colonization. Respiratory *Sa* abundance was associated with risk of incident *Sa* VAP, particularly among subjects without recognized *Sa* colonization.

Disclosures. **All Authors**: No reported disclosures

1210. K-mer Profiling Powered by Reference-assisted Assembly of NGS Data: A Highly Sensitive Protocol to Infer the Plasma Microbiome Using Cell-free DNA Sequence Data

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Session: P-54. Microbiome in Health and Disease

Background. Cell-free DNA (cfDNA) has emerged as an important clinical specimen to probe for pathogenic microbes, especially in organ transplant patients where the same data can be used to predict allograft rejection. Recent reports described viral, bacterial or the complete microbial diversity in plasma following cfDNA sequencing. The prevalence of certain viral families (anelloviridae) is associated with immunosuppressant dosage and the risk of antibody mediated rejection. While being informative, the cfDNA reads are inherently shorter in length (~160bp or 2x75bp) and predominated by the host DNA (~97-99%), causing challenges in their taxonomic annotation and lower specificity. Here we present a computational protocol which minimizes these challenges by merging the concept of "Reference-assisted Assembly" with K-mer profiles of NGS data, for highly sensitive and specific microbial detection.

Methods. We developed a pipeline in which non-host NGS data (reads not mapped to the human genome) undergo a reference-assisted assembly operation and then taxonomic annotation using KrakenUneq (a K-mer based classifier). We trained the KrakenUneq on an in-house and curated database of ~12,000 viral genomes. We used three different K-mer values (16, 21, 31) to train KrakenUneq, and final predictions are made by applying a majority-wins rule. Currently the default KrakenUneq database is used for bacterial & fungal metagenome analysis. We tested our method on 30 simulated and 124 clinical samples obtained from a biorepository.

Results. Our protocol currently screens for a targeted list of pathogens (15 viral species, 16 bacterial and 10 fungal genera). On a simulated set of viral sample mixes, our protocol had 100% accuracy. For 124 clinical samples, predictions were evaluated for specificity and sensitivity using qPCR assays for the following viral species: EBV, BKV, JCV, HSV1/2, HHV7, and CMV. Total 33/38 computational predictions (87%) were confirmed by qPCR. The prediction sensitivity in terms of cps/ml ranged from 6 - 10^6 copies/mL.