Chronic psychosocial stress in children and gut health

MICHELS, Nathalie (1); DE HENAUW, Stefaan (1); VAN DE WIELE, Tom (1)

Presented by MICHELS, Nathalie

1: Ghent University, Belgium

nathalie.michels@ugent.be

O bjectives : W e investigated the relationship between bacterial-produced short-chain fatty acids, gut barrier function and stress load. Methodology : In 113 Belgian children (8-16y), stress was measured by 3cm hair cortisol, 5-minute heart rate variability (low-to-high frequency ratio) and self-reported emotional problems and negative events. Fecal calprotectin was determined as a marker of intestinal inflammation and an indicator of gut barrier integrity. Fecal short-chain fatty acids (butyrate, propionate, acetate, valerate, isobutyrate, isovalerate) were measured. Linear regression analyses were adjusted for sex, age, socio-economic status, BMI, fiber intake and protein intake. Results: Emotional problems were significantly associated with higher butyrate (β=0.263), valerate (β=0.230), isovalerate (=0.231) and isobutyrate (β=0.233). Heart rate variability (sympatho-vagal balance) was also related to butyrate levels (β=0.253). Hair cortisol was not associated with short-chain fatty acids. None of the stress measures nor short-chain fatty acids were significantly related to fecal calprotectin. Conclusions: In healthy children, the impact of chronic stress is manifested more obviously in terms of short-chain fatty acids than in intestinal inflammation measured by calprotectin. Fecal sequencing data will be available in August to further explain the rather counterintuitive associations with butyrate. Recruitment of children with depression is ongoing to allow comparison with a clinical population.

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The Effects of Different Physicochemical Factors on Growth and Survival of Human Gut Lactic Acid Bacteria

SOGHOMONYAN, Diana (1); TRCHOUNIAN, Armen (1)

Presented by SOGHOMONYAN, Diana

1: Yerevan State University, Armenia

d.soghomonyan@ysu.am

Human gut lactic acid bacteria (LAB) are affected by different physicochemical factors such as electromagnetic irradiation (EMI), antibiotics and food preservatives, used in food processing and medicine [1]. In this work it was studied the separate and combined effects of antibiotic ceftazidime (20 μm), food preservative E-224 or potassium metabisulphite (240 mg/ml) and low intensity (0.06 mW /cm 2), extremely high frequency electromagnetic waves at the frequencies of 51.8 and 53 GHz (1h exposure) on Lactobacillus paracasei subsp. paracasei growth and survival in in vitro model of human gastrointestinal tract and in salt medium. The results show, that EMI at both frequencies and ceftazidime had oppressive effects on LAB in gastrointestinal tract model. Particularly colony forming units number was decreased ~ 3 and 1.2 fold at both frequencies, respectively, as well as the effects of E-224 are more stronger after EMI: it was ~2 fold. It was suggested that EMI increases the sensitivity of LAB to different chemicals. The results could be applied in food industry and medicine.

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Improvement of intestinal mucosa after probiotic supplementation in HIV-1 patients

SCHIETROMA, IVAN (1); GIUSTINI, Noemi (1); SERAFINO, Sara (1); CORANO SCHERI, Giuseppe (1); NAJAFI FARD, Saeid (1); DE GIROLAMO, Gabriella (1); SELVAGGI, Carla (2); FANELLO, Gianfranco (3); CECCARELLI, Giancarlo (4); ANDREOTTI, Mauro (5); SCAGNOLARI, Caro

Presented by SCHIETROMA, IVAN

1: Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy 2: Department of Molecular Medicine, Laboratory of Virology, Sapienza University of Rome, Italy 3: Digestive Endoscopy Surgical Unit, Policlinico Umberto I, Sapienza University of Rome, Italy 4: Department of Public Health and Infectious Diseases, Policlinico Umberto I, Sapienza University of Rome, Italy 5: Department of Therapeutic Research and Medicines Evaluation, Italian Institute of Health, Rome, Italy 6: Pasteur Institute of Italy, Cenci-Bolognetti Foundation, Rome 7:

Department of Molecular Medicine, Laboratory of Virology, Sapienza University of Rome, Italy

schietroma.ivan@gmail.com

Objectives : We evaluated the inflammatory infiltration and the damages of the gut epithelial in intestinal biopsies collected before and after 6 months of probiotics treatment (Vivomixx in EU;Visbiome in USA), focusing on intraepithelial lymphocytes(IELs) count, enterocytes apoptosis, and HSP60 protein in patients infected with HIV-1 on c-ART. Methodology : Ten HIV-infected subjects were underwent endoscopic procedures prior to initiation of probiotics supplementation and after 6 months. All samples were evaluated with histological score analysis, Immunohistochemical evaluation and T.U.N.E.L. for apoptosis evaluation. Results : After 6 months of probiotics supplementation, the number of IELs significantly decreased in the ileum, cecum, transverse and descending colon (p=0.049, p=0.027, p=0.004, p=0.002 respectively). The HSP60 median values were higher in all intestinal tracts before supplementations, and significantly decreased after treatment in ascending, transverse and descending colon (p= 0.01; p= 0.037; p= 0.04 respectively). The decline of IELs infiltrating the intestinal epithelium after treatment was strictly associated to a statistically significant decrease in the levels of enterocytes apoptosis index both in epithelium and intestinal crypts (p=0.04). Conclusion : probiotics supplementation for 6 months in HIV-1+ patients under ART is associated with a marked decrease in IELs and HSP60 protein, recovery of the gut epithelial integrity, and improved mitochondrial morphology.

Supported by Sapienza University of Rome

TRANSCRIPTIONAL AND FUNCTIONAL ANALYSES OF THE GENE ENCODING ANTI-INFLAMMATORY PEPTIDES BY FAECALIBACTERIUM PRAUSNITZII A2-165

BURMAN, Sriti (1); STOLL, Thomas (1); BUCZEK, Dorota (1); HILL, Michelle (1); LANGELLA, Philippe (2); O CUIV, Paraic (1); MORRISON, Mark (1)

Presented by BURMAN, Sriti

1: The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia 2: INRA Micalis Institute, Jouy-en-Josas, France

s.burman@uq.edu.au

Background and Objectives: Faecalibacterium prausnitzii is considered to be a part of the core human gut microbiome and produces “anti-inflammatory” factors, including peptides derived from the Mam protein. The genetics and regulation of this process remains unknown. The main objective of this study was to examine the expression of the mam gene, and neighbouring genes possibly involved with Mam protein processing, during the growth cycle of F. prausnitzii. Methodology: F. prausnitzii strain A2-165 was cultured using a complex medium for different periods of time to harvest cells and culture fluids representing different stages of growth. The expression of mam and neighbouring genes encoding putative peptidases were assessed by qRT-PCR, and the presence of Mam-derived peptides in culture fluids determined by mass spectrometric methods. Results: When normalised to rRNA gene expression, the mam and peptidase genes were found to be constitutively expressed, and Mam peptide abundance in the culture fluids increased with growth. We are now examining the same culture fluids for presence of the Mam protein, and their anti-inflammatory effects using human epithelial cells. Conclusions: These results suggest mam gene expression is constitutive and that Mam peptide production and release is a continuous rather than regulated process.

Supported by The University of Queensland Diamantina Institute

Probiotics supplementation modulates IFN-I/II response and their relationships with CSF-miRNAs levels in treated HIV-1 positive patients with suppressed viremia.

CORANO SCHERI, Giuseppe (1); SELVAGGI, Carla (2); GIUSTINI, Noemi (1); SERAFINO, Sara (1); SCHIETROMA, Ivan (1); CECCARELLI, Giancarlo (1); ANDREOTTI, Mauro (3); ANTONELLI, Guido (2); VULLO, Vincenzo (1); D'ETTORRE, Gabriella (1); SCAGNOLARI, Carolina (4,

Presented by CORANO SCHERI, Giuseppe

1: Department of Public Health and Infectious Diseases, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy, Italy 2: Department of Molecular Medicine, Laboratory of Virology, Sapienza University of Rome, Viale di porta Tiburtina 28, 00185 Rome, Italy, Italy 3: Department of Therapeutic Research and Medicines Evaluation, Italian Institute of Health, 00161 Rome, Italy, Italy 4: Istituto Pasteur Italia - Fondazione Cenci Bolognetti, 00161 Rome, Italy 5:

Department of Molecular Medicine, Laboratory of Virology, "Sapienza" University of Rome, 00185 Rome, Italy, Italy

giuseppe.coranoscheri@uniroma1.it

Objectives :The probiotics effects on systemic and gut associated type I interferon (IFN) immunity activation as well as on microRNA levels mediating both IFN response and CNS inflammation in HIV-1 positive patients are unclear.We evaluated the impact of probiotics supplementation (Vivomixx in EU;Visbiome in USA) for six months on the expression of all IFN-α subtypes (n=12), IFNβ and IFNγ and the relationship between IFN-I/II response and CSF-miRNAs levels in HIV-1 infected patients under cART with suppressed HIV-RNA. Methodology :Ten HIV-infected subjects underwent endoscopic procedures and blood collection prior to initiation of probiotics supplementation and after 6 months. Lamina propria lymphocyte, PBMC were isolated. CSF (Cerebrospinal fluid) was collected by lumbar puncture. IFN-α subtypes, IFNβ, IFNγ, USP18 and miR-155 and 146a expression were measured by RT/ real-time PCR. Data were analyzed by Wilcoxon test. Results :We found that IFN-I/II response is more activated in GALT than peripheral blood. The IFN-α subtypes 6,10,14,17 and 21 and IFNγ levels significantly changed in both GALT and blood after probiotic supplementation. The expression of IFN-I/II subtypes correlated with that of CSF-derived miR-155 and 146a levels. Conclusion :Our results showed that probiotics modulate significantly systemic and gut associated IFN-I/II signature influencing their relationship with CSF-miRNA levels during chronic HIV-1 infection.

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Identification of blood microbiota alteration associated with liver fibrosis in obese patients.

LELOUVIER, Benjamin (1); SERVANT, Florence (1); BURCELIN, Remy (2); AMAR, Jacques (3)

Presented by LELOUVIER, Benjamin

1: Vaiomer, France 2: Inserm, France 3: Hopital Rangueil, Toulouse, France

benjamin.lelouvier@vaiomer.com

Objective: The early detection of liver fibrosis among patients with nonalcoholic fatty liver disease is an important clinical need. In view of the role played by bacterial translocation in liver disease and obesity, we sought to investigate the relationship between blood microbiota and liver fibrosis in obese patients. Methodology: We carried out a cross-sectional study of obese patients from the cohort FLORINASH divided into a discovery cohort and a validation cohort. Blood bacterial DNA was analyzed both quantitatively by qPCR and qualitatively by 16S rDNA targeted metagenomic sequencing and functional metagenome prediction. Results: The 16S rDNA concentration was significantly higher in patients with liver fibrosis. By 16S sequencing, we found specific differences in the proportion of several bacterial taxa in both blood and feces that correlate with the presence of liver fibrosis thus defining a specific signature of the liver disease. We confirmed in the validation cohort the correlation between blood 16S rDNA concentration and liver fibrosis. Conclusions: We have shown that changes in blood microbiota are associated with liver fibrosis in obese patients. Blood microbiota analysis provides potential biomarkers for the detection of liver fibrosis in this population. Normal 0 21 false false false FR X-NONE X-NONE Normal 0 21 false false false FR X-NONE X-NONE Normal 0 21 false false false FR X-NONE X-NONE

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Zebrafish gut as a house for human intestinal bacteria

ARIAS JAYO, Nerea

Presented by ARIAS JAYO, Nerea

Azti tecnalia, Spain

narias@azti.es

The human gut houses a vast microbial community that is vital for maintaining host health. The complexity and the high inter-individual variability of the human gut microbiota are inherent problems in the study of host-microbe interactions. Gnotobiotic animals offer the opportunity to circumvent some problems. For that reason, it would be desirable to have a simple animal model to study the interactions between the gut microbiota and the host (1). We have colonized the intestine of 5 days post fertilization (dpf) zebrafish larvae with five bacterial members of the human gut microbiome (E. coli, E. faecalis, B. breve, L. casei and E. limosum). Axenic zebrafish larvae are infected with the bacterial consortia during 48 hours. The colonization is monitorized with different culture media and -q-PCR analysis. All the strains remain in the zebrafish gut almost during 48 hours post infection (hpi). As a matter of fact, we resolved that different bacteria commonly found in the human intestine, including obligate anaerobes, are able to colonize and compete into the zebrafish intestine. This suggests that the developing zebra fi sh could be a suitable model for studying the human gut microbiota (2). 1. Rawls J. Cell.2006;127(2):423-433 2. Seth A. Disease models & mechanisms.2013;6(5):1080-1088 .

The antigen HC-NAP promotes inflammatory-dependent mechanisms responsible for atherosclerosis progression in Helicobacter cinaedi-infected patients

D'ELIOS, Mario Milco (1); VALLESE, Francesca (2); BENAGIANO, Marisa (1); BERNARDINI, Maria Lina (3); FERRARI, Mauro (4); ZANOTTI, Giuseppe (2); DE BERNARD, Marina (5); CODOLO, Gaia (5)

Presented by CODOLO, Gaia

1: Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy 2: Department of Biomedical Sciences, University of Padua, Padua, Italy 3: Department of Biology and Biotechnology, “C. Darwin” and Institute Pasteur Italy - Fondazione

Cenci Bolognetti- Sapienza University of Rome, Rome, Italy 4: Vascular Surgery Unit, Cisanello University Hospital AOUP, Pisa, Italy 5: Department of Biology, University of Padua, Padua, Italy

gaia.codolo@unipd.it

Objective : One emerging paradigm suggests microbial infections as promoter of inflammation and immune reactions in atherosclerosis 1 . Unlike other bacterial pathogens propoted of having a role in atherosclerosis, Helicobacter cinaedi (Hc) displays a strong vascular tropism and localization of Hc antigens in human atherosclerotic tissues has been documented 2 . This study was undertaken to evaluate the role of the neutrophil-activating protein (HC-NAP) in triggering the inflammatory process in Hc-associated atherosclerosis. Methodology : HC-NAP seroconversion was analyzed in atherosclerotic patients. Cytokine profile of carotid artery plaques T cells HC-NAP-specific was investigated in patients with atherosclerosis. The cytokine and chemokines profile induced by HC-NAP in macrophages, monocytes and endothelial was also evaluated; as well as the HC-NAP-induced macrophages phenotypic profile. Results : We show that HC-NAP promotes the differentiation and maintenance of the pro-inflammatory profile of human macrophages and triggers the formation of foam cells; it also increases the adhesiveness of endothelial cells and stimulates them to release chemokines recruiting mononuclear cells. At least 27% of patients with atherosclerosis are seropositive for HC-NAP and in their lesions HC-NAP-specific T cells are present and drive a Th1 inflammation. Conclusions : Our results identify HC-NAP as a key factor for the pathogenesis of atherosclerosis associated to Hc infection.

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Curing/Remission of Multiple Autoimmune Diseases is Possible by Manipulation of the Human Gut Microbiome: The Effect of a Lectin Limited, Polyphenol Enriched, Prebiotic/Probiotic Regimen in 78 patients

Presented by GUNDRY, Steven

1: The Centers for Restorative Medicine, The International Heart and Lung Insitute,

Palm Springs and Santa Barbara, California, USA, United States

DrGundry@Gmail.com

Autoimmune diseases (AI) are increasing rapidly, suggesting a penetration of the gut wall by molecular mimicking proteins and bacterial cell walls LPS's. Based on our study of plant lectins and Casein A1 milk proteins penetrating the gut wall to stimulate an immune response via molecular mimicry to similar proteins in skin, nerves, thyroid, and synovial membranes, we treated 78 consecutive patients with Rheumatoid Arthritis, Multiple Sclerosis, Lupus(SLE), Crohn's, Colitis, Psoriasis, Sjogren's Syndrome, Hashimoto's, Scleroderma, etc. Most took immunosuppressants . Treatment consisted of removal of lectin containing food groups: grains, pseudograins, beans, nightshades, peanuts, cashews, squashes and Casein A1 products (the Matrix Protocol); repopulation and reeducation of Gut flora using BC30, daily Prebiotic powder (PrebioThrive), Polyphenol supplements (Vital Reds), high dose Vit D3, and a diet with resistant starches. Inflammatory markers of hs-CRP, IL-6, TNF-alpha, IL-17A, were measured q 3 months. Patients achieved cure in 68/78 (87%) with withdrawal of drugs, or remission (some drug use) in 10/78 (13%). 15/78 pts (19%) had relapse when lectins were reintroduced, but resolved with removal. Conclusions: AI, a manifestation of disturbed gut microbiome-immune system-enterocyte interaction, can be reversed/cured by a lectin limited diet, supplemented with spore forming bacteria, prebiotics, and polyphenols.

MICROBIOTA DYSBIOSIS INDUCED BY DEFECT OF ENTERIC ANTIMICROBIAL ACTIVITY TRIGGERS VISCERAL HYPERSENSITIVITY IN YOUNG ADULT MICE

RIBA, Ambre (1); OLIER, Maïwenn (1); LACROIX-LAMANDé, Sonia (2); LENCINA, Corinne (1); BACQUIé, Valerie (1); HARKAT, Cherryl (1); GILLET, Marion (1); SOMMER, Caroline (3); SALVADOR-CARTIER, Christel (4); LAURENT, Fabrice (2); THEODOROU, Vassilia (1); MENA

Presented by MENARD, Sandrine

1: INRA Toxalim Team 4, Toulouse, France 2: Equipe Apicomplexes et Immunité Mucosale (AIM), UMR 1282 INRA/Université-Infectiologie et Santé Publique (ISP), Centre INRA Val de Loire, Nouzilly, France 3: INRA Toxalim Team 21, Toulouse, France 4: INRA Toxalim Team 11, Toulouse, France 5: INRA, France

sandrine.menard@toulouse.inra.fr

Paneth cell-derived antimicrobial peptides like lysozyme provide antibacterial protection and maintain intestinal homeostasis. In this study, we analyzed the consequences of altered Paneth cells function on fecal antimicrobial activity, intestinal homeostasis and visceral sensitivity at adulthood. In 50-days old Sox9 flox/flox -vil-Cre female mice, absence of Paneth increased fecal population of Enterobacteriaceae associated to visceral hypersensitivity. Daily gavage of conventional adult mice with 10 9 commensal Escherichia coli , induced visceral hypersensitivity. Occurrence of adverse events during neonatal period is known to impair intestinal homeostasis establishment. Maternal separation (MS) is a well described rodent model of psychological stress characterized by a decrease of intestinal secretory cells and visceral hypersensitivity mimicking what we observed in Sox9 flox/flox -vil-cre mice. We wondered if in this model we also observed a dysbiosis in favor of Enterobacteriaceae. Mice submitted to MS, presented a defect of fecal antimicrobial activity associated with a fecal overgrowth of Enterobacteriaceae . Furthermore, this antimicrobial defect and its consequences on visceral sensitivity were prevented by an oral administration of lysozyme. Altogether our results show that a defect of enteric antimicrobial functions leads to microbiota dysbiosis in favor of Enterobacteriaceae responsible for visceral hypersensitivity providing new mechanistic insights in maternal separation-induced visceral hypersensitivity

Colonic bacteria and methanogens specificly response to different types of dietary fibers through the alteration of community, fermentation mode and metablic pathyways in swine and mice model

LUO, Yuheng (1); ZHANG, Ling (1); SMIDT, Hauke (2); WRIGHT, André-Denis (3); LI, Hua (1); ZHAO, Yao (1); CHEN, Daiwen (1)

Presented by LUO, Yuheng

1: Sichuan Agricultural University, China 2: Wageningen University, Netherlands 3: University of Arizona, United States

luoluo212@126.com

Fermentability of dietary fibers (DF) in the hindgut depends on their structures. We carried out a series of trials to investigate the influence of different types of DF, pea fiber (PF), β-glucan (G) , microcrystalline cellulose (MCC), and mixture of G and MCC (GM), on the community and function of colonic microbes of monogastric animals. In pigs, the acetate ratio was significantly higher but butyrate ratio lower in PF group than control, with Prevotella as predominant bacteria and increased bacteria involved in DF degradation ($P < 0.05$). PF also resulted in the increase of hydrogenotrophs ($P < 0.05$), and the methanongens shift from Methanobrevibacter to Methanomassiliicoccus -like genus (Fig.1) . Y east β-glucan significantly increased M. ruminantium and M. wolinii in fermented porcine colonic digesta. In BALB/c mice fed with G diet, colonic bacterial α-diversity was lower than M or GM. Bacteroidetes / Firmicutes was significantly increased ($P < 0.01$), with an increase of Bacteroides , Dehalobacterium and Prevotella . Bacteria in group G were characterized by a lower abundance/prevalence of genes conferring resistance to drugs except for β-lactam antibiotics (Fig.2). Cross-feeding of bacteria and methanogens may be a key point to understand the utilization of different DF (Fig. 3).

InterceptingHost Microbial Signalling for Prevention of Chronic Pathogen Establishment in Respiratory Disease Microbiomes .

O'GARA, Fergal (1); O'GARA, Fergal (2); REEN, Jerry (3)

Presented by O'GARA, Fergal

1: National University of Ireland Cork., Ireland 2: 1 BIOMERIT Research Centre, School of Microbiology, University College Cork - National University of Ireland, Cork, Ireland.

2 School of Biomedical Sciences, Curtin Health Innovation Research Institute, Curtin University, Perth, WA 6102, Australia., Ireland 3: Biomerit Research Centre, Ireland

f.ogara@ucc.ie

Despite aggressive antimicrobial therapy, many respiratory pathogens persist in the lung, underpinning the chronic inflammation and eventual lung decline that are characteristic of respiratory disease. Early clinical interventions that prevent pathogens from entering this chronic persistent lifestyle are key to the effective management of chronic infections and associated inflammation. Recently, bile acid aspiration has emerged as a major comorbidity associated with a range of lung diseases, shaping the lung microbiome and promoting colonisation by Pseudomonas aeruginosa in Cystic Fibrosis (CF) patients. Bile signaling was shown to elicit chronic biofilm behavior and modulate antibiotic tolerance in respiratory pathogens, including P. aeruginosa and Staphylococcus aureus , suggesting adaptation of the host microbiome to the presence of this important host factor. Global expression profiling and functional genomics revealed insights into the molecular mechanism underlying this response. Therapies that prevent the aspiration of this key host trigger into the lungs of patients with respiratory disease could be effective in combatting the onset of chronic disease. Furthermore, the tandem development of small molecular therapeutics that intercept the formation of biofilms by microbial pathogens, without disturbing the homeostasis of the host microbiome, is of crucial importance.

The gut microbiota mobilome in preterm infants with and without necrotizing enterocolitis

RAVI, Anuradha (1); ESTENSMO, Eva Lena (1); L'ABéE-LUND, Trine (1); FOLEY, Steven (2); ALLGAIER, Bernhard (3); MARTIN, Camilia (4); CLAUD, Erika (5); RUDI, Knut (1)

Presented by RAVI, Anuradha

1: Norwegian University of Life Sciences, Norway 2: Food and drug admnistration, United States 3: NorthShore University HealthCenter, United States 4: Beth Israel Deaconess Medical Center, United States 5: The University of Chicago, United States

anuradha.ravi@nmbu.no

Objective: To investigate the association between the mobilome, necrotizing enterocolitis and hospital. Study Design: Fecal samples were collected from preterm infants with and without NEC taken from Boston, Chicago and Evanston. The gut microbiomewas classified using 16S rRNA gene (V3-V4) metagenome sequencing and QIIME pipeline to generate Operational Taxanomic Units (OTUs). Shotgun metagenome sequencing and analysis was done for selected samples using Geneious software. Finally, quantitative PCR screenings for plasmid signature genes. Fisher Exact test, Pearson correlation and binomial testing were used for pairwise comparisons. All statistical analyses was performed using MATLAB® software (The MathWorks Inc., USA). Results: From the 16S rRNA gene analyses, the microbiota (β diversity) was significantly different between NEC positive and NEC negative infants and between NEC and hospital. Shotgun metagenome analyses for selected samples showed genes related to conjugative plasmids and several antibiotic resistance genes. In addition, we assembled a potential complete conjugative plasmid carrying multidrug resistance genes (integron) and virulence genes. Quantitative PCR targeting the plasmid signature genes showed the institution in Evanston with higher prevalence compared to Boston and Chicago. Conclusion: Our results point toward the importance of the mobilome in preterm infants with respect to both hospital differences and NEC association.

The effects of intracolonic indole and hydrogen sulfide, gut-bacteria metabolites, on the circulatory system in rats.

UFNAL, Marcin (1); DRAPALA, Adrian (2); TOMASOVA, Lenka (3); KONOPELSKI, Piotr (2); PHAM, Kinga (2)

Presented by UFNAL, Marcin

1: Department of Experimental Physiology and Pathophysiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, Warsaw, Poland,, Poland 2: Department of Experimental Physiology and Pathophysiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, Warsaw, Poland, Poland 3: Department of Experimental Physiology and Pathophysiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, Warsaw, Poland, Slovakia

mufnal@wum.edu.pl

Normal 0 false false false PL X-NONE X-NONE Objectives : Increasing evidence suggests that hypertension is associated with gut microbiota dysbiosis; however, the involvement of the gut microbiota in the control of arterial blood pressure is not determined. Hydrogen sulfide (H 2 S) and indole are abundant metabolites of gut bacteria in mammals. The goal of the study was to evaluate the effects of intracolonic indole and H 2 S on arterial blood pressure, heart rate and electrical activity of the heart. Methods : Arterial blood pressure and ECG were recorded in anesthetized, male, 16-week old, normotensive Wistar Kyoto rats at baseline and after intracolonic injection of either saline (controls) or indole or Na 2 S. Results: Both, indole and the H 2 S donor produced a significant, dose-dependent decrease in mean arterial blood pressure. We found no apparent cardiotoxic effects of the gut bacteria-derived compounds. Conclusions: Our study shows that intracolonic H 2 S and indole may contribute to the control of arterial blood pressure and etiology of hypertension.

Supported by Medical University of Warsaw

Revealing insights into the composition of the vaginal microbial community structure in Korean woman

LIM, Sooyeon (1); LEE, Sung Ki (2); KIM, Byoung-Chan (1)

Presented by LIM, Sooyeon

1: Korea Research Institute of Bioscience and Biotechnology (KRIBB), Republic Of Korea 2: Department of Obstetrics and Gynecology, College of Medicine, Konyang University, Republic Of Korea

limsooy@snu.ac.kr

Low birth rate is a matter of concern these days. Therefore plenty of studies have examined the vaginal microbiota which are key components of a woman's healthy and pregnancy. In this study, we collected total 137 vaginal samples from Korean woman and we focused on spontaneous abortion, preterm birth and high risk pregnancy using several bioinformatics tools. Comparison of community structure between normal woman and high risk pregnancy woman showed significant differences. For normal woman, Lactobacillus inners and Lactobacillus crispatus were clearly distinguished as a dominant species. Especially, L.crispatus was represent of the normal group. In all samples, total 700genera and 1,494species existed. But interestingly, total 600genera and 1300species revealed within the high risk pregnancy woman. These result showed the composition of the vaginal microbiota of normal pregnant women is very simple and similar each other. Also 46 of the habitual abortion woman, 6 of whom delivered preterm and 3 of whom miscarried. Those microbiota were much more diverse than normal woman and a normal delivery woman even belong to the habitual abortion woman. DiGiulio, D. B. et al. Temporal and spatial variation of the human microbiota during pregnancy. PNAS 112,11060-65 (2015).

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Structuring genetic and taxonomic diversity in gut microbes of lizards affected by a quick dietary change.

VIGLIOTTI, Chloé (1); BAPTESTE, Eric (2); HABIB, Michel (3); HERREL, Anthony (4); LOPEZ, Philippe (5)

Presented by VIGLIOTTI, Chloé

1: CNRS UMR 7138, 7179, France 2: UMR 7138 Evolution Paris Seine, Université Pierre et Marie Curie, 75005 Paris, France – supported by an ERC grant FP7/2007-2013 Grant Agreement # 615274, France 3: LIAFA, UMR 7089 CNRS & Université Paris Diderot - Paris 7, France, France 4: UMR 7179, CNRS/MNHN, Département d'Ecologie et de Gestion de la Biodiversité, Paris Cedex, France, France 5: UMR 7138 Evolution Paris Seine, Université Pierre et Marie Curie, 75005 Paris, France, France

chloe.vigliotti@agroparistech.fr

P { margin-bottom: 0.21cm; } 35 years ago, ecologists introduced 10 insectivorous lizards from the islands of Pod Kopiste to that of Pod Mrcaru [1] . Podarcis sicula on Pod Mrcaru became omnivorous (80% herbivorous)[2] and changed in morphology[3]. However, changes of their gut microbiome/microbiota were not investigated. We sequenced 32 samples from guts of insectivorous and omnivorous lizards by Illumina Miseq to test whether (i) changes in microbial communities[4] and (ii) functional acquisition/loss of microbiome gene families were associated with the dietary shift[5]. We used multivariate analyses and innovative network models (reads similarity, unifrac networks) to analyze variations in microbiota/microbiomes. During this dietary shift, the abundance of few microbial taxa (e .g. genera Clostridium sensu stricto and Treponema are more abundant in omnivorous than in insectivorous lizards.) and few key metabolic genes changed (the biotin enzyme of the biotin metabolism pathway, involved in legume degradation). Thus specific changes in the microbiome correlate with major changes in the hosts phenotypes. The use of this additional vertebrate non mammalian model, with a rapid generation time, provides a novel perspective to assess the generality of findings regarding dietary shift effects in human microbiome studies.

Supported by LabexBCDIV

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TSI - a low volume small intestine in vitro model with increased throughput

CIEPLAK, Tomasz (1); WEISE, Maria (1); NIELSEN, Sandris Dennis (1); VAN DER BERG, Winfried J Franciscus (1)

Presented by CIEPLAK, Tomasz

1: University of Copenhagen, Denmark

tomasz.cieplak@good.ku.dk

Normal 0 false false false EN-US JA X-NONE Objectives: Aim of this study was to create small volume high throughput in vitro model of small intestine (SI) as a screening platform for studying digestion of food, survival of bacteria and absorption of drugs and small nutrients. Methodology: The TSI basic module consists of 5 reactors, with a working volume of 10ml. During simulated passage of SI, bile was absorbed and pH adjusted to physiological relevant values in duodenum, jejunum and ileum. Furthermore, a consortium of six important bacterial members of the ileal microbiota is included in the ileal step of the model. The TSI model was validated by testing survival of three probiotic bacteria strains and compared against validated static digestion model (1). Results: The Smallest Intestine in vitro model (TSI) was created and was able to simulate conditions in human small intestine. Moreover survival of probiotic bacteria measured shows strong correlation with results obtained using validated static in vitro protocol. Conclusion: The TSI enables to test large amount of samples, cheap and in relatively short time. Multiples of five reactors can be added to increase numbers of biological and technical replicates. It proves to be an efficient way of testing survival of probiotic bacteria in SI.

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Infant Gut Mycobiota and Fungal Transfer from Mother to Child

SCHEI, Kasper

Presented by SCHEI, Kasper

NTNU Norwegian University of Science and Technology, Norway

kasperschei@gmail.com

INTRODUCTION: The fungi in the gastrointestinal tractus (gut mycobiota) have now become recognised as a significant part of the gut microbiota and may well be of importance in human health.(1) In contrast to the adult gut mycobiota, the establishing infant gut mycobiota has never been completely described before, and no one has looked at fungal transfer between mother and child. MATERIAL AND METHOD: In this prospective cohort, we followed 298 pairs of healthy mothers and offspring at term until two years of age (1516 samples) and we explored the gut mycobiota connection. We measured fungal quantity in all samples and Illumina sequenced 92 samples to investigate which species that host the infant gut. RESULTS: There was an increased chance that newborns have detectable fungal DNA in their faeces if the pregnant mother had detectable fungal DNA as well (OR = 3.62, 95 % CI: 1.22-10.78). Pregnant women had the most fungal DNA in their faeces; and during the two first years, the newborn infants were most hosted by fungi. The fungal species were characterised and showed differences in alpha and beta diversity. CONCLUSION: This study gives a first insight into the fungal establishment in the newborn gut.

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Intestinal Atrophy Following Ileostomy is Associated with Dysbiosis

BEAMISH, Leigh Emma (1); JOHNSON, Judith (2); SHAW, Elisabeth (3); SCOTT, Nigel (4); BHOWMICK, Arnab (2); RIGBY, Rachael (1)

Presented by BEAMISH, Leigh Emma

1: Lancaster University, United Kingdom 2: Lancashire Teaching Hospitals Trust, United Kingdom 3: Lancaster University, 4: ,

e.beamish@lancaster.ac.uk

Surgical intervention to remove colon tumours, commonly requires inserting a temporary stoma upstream to allow tissue healing, with the aim of rejoining the bowel ~12 months later. Defunctioned bowel becomes atrophied and fibrotic, making reversal surgery difficult and delaying functional recovery. This study aimed to investigate the microbial changes that occur following enteral nutrient diversion. Intrapatient comparisons between functional and defunctioned ileal tissue, including histological assessment of morphology and epithelial cell proliferation, were performed. Mucosal-associated microflora was quantified via 16S rRNA gene copy number analysis. Luminal-associated microflora was profiled via DGGE with Sanger sequencing and qPCR analysis to genus and phylum level, respectively. Reduced villus length 47% ± 3% (n=9, $p \leq 0.001$) and proliferation 23.7% ± 3.6% (n=5, $p \leq 0.01$) confirmed atrophy of the defunctioned ileum. DGGE analysis revealed that the microflora within defunctioned ileum is less diverse and convergence between patient flora patterns was observed. Notably Clostridia and Streptococcus were reduced in relative terms in defunctioned bowel. Ileostomy-associated nutrient deprivation results in dysbiosis and impaired intestinal function in the defunctioned ileum. Altered host-microbial interactions at the mucosal surface likely contribute to the deterioration in function and strategies to sustain the microflora prior to reanastomosis should be investigated.

Supported by Bowel Cancer Research, University Hospitals of Morecambe Bay

Shotgun sequencing of total RNA as a novel method to define microbiota community structures

COTTIER, Fabien

Presented by COTTIER, Fabien

Agency for Science, Technology and Research (A*STAR), Singapore

fabien_cottier@immunol.a-star.edu.sg

Available technologies for microbiota characterisation are based on DNA sequencing of either randomly fragmented genomes (shotgun metagenomics) or PCR-amplified loci (16S/ITS amplicon sequencing). We developed a novel approach for the characterization of complex microbial communities based on shotgun sequencing of total RNA, 80% of which is represented by ribosomal RNA (rRNA) and is enriched in metabolically active cells. The method consists of: (i) an unbiased RNA extraction protocol for detection of both bacteria and fungi, (ii) a RNA-seq library preparation protocol for sequencing of large rRNA fragments, and (iii) a bioinformatic analysis pipeline to assign sequenced reads at different taxonomic levels. We benchmarked this method against existing DNA-based sequencing approaches on human stool samples spiked in with known amounts of fungal and bacterial species, allowing us to evaluate the sensitivity, linearity, cost and reproducibility of each technology. In comparison to amplicon-based sequencing, there are no PCR primer and amplification biases. In comparison to shotgun metagenomics, we demonstrate lower cost and an improved ability to detect fungi. This new method is expected to provide a more complete picture of microbial communities and to allow deeper insights into inter-species dynamics and trans-kingdom interactions within microbiome.

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The prevalence of Fusobacterium nucleatum before and after periodontal treatment of periodontitis patients in Taiwanese

WU, CHINGZONG (1); WU, Wen-Chih (2); HARADA, Fumiya (2); OU, Ken-Liang (3); YUAN, Rey-Yue (4)

Presented by WU, CHINGZONG

1: TAIPEI MEDICAL UNIVERSITY COLLEGE OF ORAL MEDICINE & TAIPEI MEDICAL UNIVERSITY HOSPITAL.

LO-TUNG POH-AI HOSPITAL, Taiwan, Province of China 2: TAIPEI MEDICAL UNIVERSITY COLLEGE OF ORAL MEDICINE, Taiwan, Province of China 3: TAIPEI MEDICAL UNIVERSITY COLLEGE OF ORAL MEDICINE, 4: Taipei Medical University College of Medicine

& Taipei Medical University Hospital, Taiwan, Province of China

chinaowu@tmu.edu.tw

The Fusobacterium nucleatum is the pathogens not only in periodontitis but also in cardiac infection ((Socransky and Haffajee, 2002 .) F. nucleatum may serves as an enabler to other microrganisms to spread systemically (Yann Fardinin et al 2011) The purpose of this study is to find the prevalence of the F.nucleatun in periodontitis before and after scaling and root planning and to find the efficacy of periodontal treatment to eradicate the pathogens . Nineteen severe adult periodontitis patients were included and approved by ethic review board. The bacteria were sampling from saliva and pocket via paper point respectively before and 4-6 weeks after scaling and root planning. The collected samples were processed by RT-PCR to quantify the microbes. The result indicated high percentage of periodontitis patients (>98%) having F.nucleatun in high amount not only in saliva (220,167) but also in periodontal pocket area (721,058). The total amount of F. nucleatun decreased dramatically in amount not only in saliva (50 %) but also in pocket (79%) after periodontal treatment . In conclusion , delicate periodontal treatment can eradicate effectively the possible oral cavity pathogens which could be harmful to cardiovascular system.

Supported by Lo-Tung Poh-Ai Hospital Taiwan

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Chemotherapy Impact on the Gut Microbiome of Patient-Derived Tumor Xenograft Models

PENSEC, Cindy (1); DE MARTINO, Alessandra (1); CONSORTIUM, IMODI (2); LE FRESNE, Sophie (1); GROH, Audrey (3); AMOUZOU, Yao (1); LEUILLET, Sébastien (1); GUENOT, Dominique (3); CAMPONE, Mario (4); CARTON, Thomas (1); LE VACON, Françoise (1)

Presented by LE VACON, Françoise

1: Biofortis Mérieux NutriSciences, France 2: http://www.imodi-cancer.org/, France 3: EA 3430, University of Strasbourg, France 4: UMR890, CRCNA, University of Nantes-Angers, France

francoise.le.vacon@mxns.com

The French consortium IMODI (Innovative MODels Initiative) including 18 partners, aims to develop predictive preclinical models for new chemotherapeutic treatment discovery, to progress toward personalized medicine. These mouse models, named Patient-Derived Tumor Xenograft (PDX) [1], are well characterized and concern 9 types of human cancer. In the last decade, the gut microbiota has been recognized as a powerful environmental factor that could influence the cancer development and therapeutic responses[2]. In IMODI project, Biofortis Mérieux NutriSciences explores the chemotherapy impact on the gut microbiota of PDX models. Having established PDX models, mice were treated with chemotherapeutic agents. Stool analyses were assessed from 4 sampling times: Before treatment/ End of treatment/ One week post-treatment/ End of experiment. The gut microbiota composition was studied by 16S rRNA genes metasequencing and the taxonomic classification of sequences was obtained using a Biofortis in-house bioinformatic pipeline based on Mothur software [3]. We will present our involvement in IMODI project and our first result about the impact of some chemotherapeutic agents on the gut microbiota composition. Microbiota represents an important additional “indicator” for evaluating the efficacy and the toxicity of pharmacological treatment that should be taken into account in the development of new therapeutic molecules

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Long lasting effect of skin microbiome modulation induced by probiotic solution application

PAETZOLD, Bernhard

Presented by PAETZOLD, Bernhard

University clinic Magdeburg,

S-Biomedic, Germany

Bernhard.Paetzold@med.ovgu.de

I n many chronic skin diseases the composition of the skin microbiome differs from that of healthy skin. Gut microbiome modulation, through fecal transplantation, have proven as a valid therapeutic strategy in diseases such as Clostridium difficile infections. Therefore techniques f or the directed modulation of the human skin microbiome may become a potential therapeutic strategy for the treatment and study of skin diseases which are associated with a dysbiosis of the skin microbiome. We have demonstrated that we can modulate the skin microbiome composition. We show that after sequential applications of a donor skin microbiome, the composition of the recipient skin microbiome becomes similar to the donor. We followed 12 subjects for multiple weeks. After interrupting the application of a donor microbiome, we observe an initial phase dominated with abundance of donor strains, and we observe a large scale microbiome re-organization that lasts up to several weeks. Directly modulating the skin microbiome by applying natural skin bacteria is possible. The observed effect is longer lasting than the application of the bacteria. This opens opportunities to develop microbiome based therapies for diseases associated with strong alterations of the skin microbiome

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Endotoxin-producing Gut Opportunistic Pathogens as Causative Agents for Human Obesity

FEI, Na (1); BRUNEAU, Aurélia (1); GéRARD, Philippe (1); ZHAO, Liping (2)

Presented by FEI, Na

1: Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay, France 2: Shanghai Jiao Tong University, China

feina405@gmail.com

O bjectives, gut microbiota has been shown a pivotal role in obesity, but it remains a challenge for demonstrating the causality of its specific functional members. Enterobacter cloacae B29 was the only example of gram-negative opportunistic pathogen s overgrowing in an obese human gut demonstrated to induce obesity and related metabolic disorders when mono-associated with germ-free mice . Methodology and Results, here we show that other g ut bacteria with high endotoxin activity, such as Escherichia coli and Klebsiella pneumoniae , also exhibited this obesogenic capacity . This capacity was not shared by all gram-negative bacteria as Bacteroides thetaiotaomicron did not induce obesity in germ-free mice. Deletion of waaG gene in lipopolysaccharide (LPS) synthetic pathway completely abolished the obesogenic capacity of B29 . Furthermore, TLR4 -/- MyD88 -/- germ-free mice resisted most of the B29 induced metabolic disorders, further demonstrating the critical role of proinflammatory LPS signaling pathway in obesity. C onclusion, Thus, endotoxin-producing opportunistic pathogens in human gut may work as causative agents in obesity.

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Oral Neisseria tropism and persistence from metagenomic sequencing data

DONATI, Claudio

Presented by DONATI, Claudio

Fondazione Edmund Mach, Italy

claudio.donati@fmach.it

Microbial epidemiology and population genomics have previously been carried out near-exclusively for organisms grown in vitro. Metagenomics helps to overcome this limitation, but it is still challenging to achieve strain-level characterization of microorganisms from culture-independent data with sufficient resolution for epidemiological modelling. Here, we have developed multiple complementary approaches that can be combined to profile and track individual microbial strains. To specifically profile highly recombinant neisseriae from oral metagenomes, we integrated four metagenomic analysis techniques: single nucleotide polymorphisms in the clade's core genome, DNA uptake sequence signatures, metagenomic multilocus sequence typing and strain-specific marker genes. We applied these tools to 520 oral metagenomes from the Human Microbiome Project, finding evidence of site tropism and temporal intra-subject strain retention. Although the opportunistic pathogen Neisseria meningitidis is enriched for colonization in the throat, N. flavescens and N. subflava populate the tongue dorsum, and N. sicca, N. mucosa and N. elongata the gingival plaque. The buccal mucosa appeared as an intermediate ecological niche between the plaque and the tongue. The resulting approaches to metagenomic strain profiling are generalizable and can be extended to other organisms and microbiomes across environments.

INFLUENCE OF PROBIOTICS ON INFLAMMATION IN PATIENTS(PTS) ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS(CAPD)

YONOVA, Diana (1); TRENDAFILOV, Ivan (1); GEORGIEVA, Ina (1); PAPAZOV, Velimir (1); TCAKOVA, Adriana (2)

Presented by YONOVA, Diana

1: Medical University Dialysis Center, Sofia, Bulgaria 2: Medical University Lab, Sofia, Bulgaria

yonovad@gmail.com

Introduction. Some inflammatory markers: IL-6,TNF-α are frequently elevated in dialysis patients and can predict cardiovascular and all-cause mortality. Endotoxin is another proved marker of inflammation in these patients. The aim. This pilot study tested impact of oral probiotics on some cytokines and endotoxin in CAPDpts. Material and metods. 2 groups of pts were tested in 5 months: 1 st group(15 CAPDpts) received 3 capsules/daily probiotics(daily dose: cfu 2.4x10(9) Lactobacillus acidofilus; cfu 3.5x10(9) Lactobacillus Bulgaricus; cfu 2.4x10(9) Streptococcus thermophilus ; cfu 0.50x10(9) Bifidobacterium spp, 600 mg prebiotic-Inulin); 2 nd group(12 CAPDpts) didn't take probiotics at all. Serum TNF-α, IL-6, IL-10 and endotoxin were measured at start and end of thestudy. Decline of residual renal function and peritonitis were also recorded. Results. In group 1 TNF-α, IL-6, and endotoxin significantly decreased($p<0.01$), while IL-10 increased($p<0.05$)in 5 months. No such changes were registered in group2. The residual renal function was preserved in patients receiving probiotics($p<0.05$). Conclusion: The probiotics could significantly reduce serum endotoxin, pro-inflammatory cytokines(TNF-α;IL-6), increase anti-inflammatory cytokine(IL-10), and maybe preserve residual renal function in CAPDpts.

Supported by Medical University Grant 2013

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Living environment modifies the mouse microbiota and alleviates allergic inflammation

OTTMAN, Noora (1); SUOMALAINEN, Alina (1); LEHTIMäKI, Jenni (1); LEHTO, Maili (2); KARISOLA, Piia (1); HANSKI, Ilkka (1); RUOKOLAINEN, Lasse (1); FYHRQUIST, Nanna (1)

Presented by OTTMAN, Noora

1: University of Helsinki, Finland 2: Finnish Institute of Occupational Health, Finland

noora.ottman@helsinki.fi

Contact with environmental biodiversity, including microbial communities, has been suggested to be protective against allergies(1,2). The aim of this study is to understand how the living environment influences immunological parameters through modifying the mouse gut microbiota. Mice were kept on either soil, straw/sheep bedding, or in standard mouse-housing environment for 12 weeks, followed by exposure to the murine lung inflammation protocol, after which samples for 16S rRNA sequencing and immunological analyses were collected. We find that the living environment influences the mouse microbiota considerably. While Firmicutes was the dominant phylum in the fecal microbiota of mice in the standard environment, Bacteroidetes was the most abundant phylum in soil and straw environments. This switch was largely due to an increase in the abundance of one Bacteroidales family (S24-7). While the role of this family is unclear, it has been suggested to be involved in host-microbe interactions affecting gut health(3). In our study, anti-inflammatory signalling was upregulated in the mouse ileum in the soil group compared to other groups. The fecal microbiota of the soil group was depleted in Alistipes , associated with both healthy(4) and diseased gut(5). In conclusion, changes in living environments have major effects on mouse microbiota and immunological parameters.

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Associating a specific gut microbiome with kidney stone disease

DAVIES, Paul Kelvin (1); MOAZAMI, Saman (2); CHEN, Zigui (3); AGALLIU, Ilir (1); BURK, Robert (1); STERN, Joshua (2)

Presented by DAVIES, Paul Kelvin

1: Albert Einstein College of Medicine, United States 2: Montefiore Medical Center, United States 3: The Chinese University of Hong Kong, Hong Kong

kelvin.davies@einstein.yu.edu

OBJECTIVES: The relationship between the gut microbiome (GMB) and kidney stone disease (KSD) has not been investigated. In this pilot study we identify differences in the GMB between patients with or without KSD. METHODOLOGY: 23 patients with KSD and 6 controls were enrolled into our IRB approved pilot study. Bacterial abundance in fecal specimens was determined by analysis of 16s rRNA marker gene sequences using next generation sequencing. RESULTS: Sequencing of the GMB identified 178 bacterial types at the genus level. The 5 most abundant enterotypes made up greater than 50% of the total bacterial abundance. Bacteroides genus was 3.4-fold more abundant in the KSD group compared to controls (34.9% vs 10.2%, p=0.001) whereas Prevotella genus was 2.8-fold more abundant in the control group compared (34.7% vs 12.3%; p=0.033). In a multivariate analysis including age, gender, BMI, and diabetes, there was a positive association between KSD and high prevalence for Bacteroides (OR=3.26, p=0.033), whereas there was an inverse association with Prevotella (OR=0.37, p=0.043). CONCLUSIONS: These preliminary studies have identified two genera of bacteria in the GMB that had significant association with KSD providing for the first time evidence associating differences in the GMB with KSD.

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Changes in the Lung Microbiome in Relation to Anti-pseudomonal Therapy in Children With Cystic Fibrosis

KRAMNá, Lenka (1); DřEVíNEK, Pavel (2); LIN, Jake (3); KULICH, Michal (4); CINEK, Ondřej (1)

Presented by KRAMNá, Lenka

1: Department of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic, Czech Republic 2: Department of Medical Microbiology, 2nd Faculty of Medicine Charles University in Prague and University Hospital Motol, Prague, Czech Republic, Czech Republic 3: University of Tampere, BioMediTech, Computational Biology, Tampere, Finland, Finland 4: Department of Probability and Mathematical Statistics, Faculty of Mathematics and Physics, Charles University, Prague, Czech Republic

lenka.kramna@lfmotol.cuni.cz

Background: Our aim was to assess changes in the lung microbiome in children with CF that were induced by antibiotic therapy against the most important of the pathogens, Pseudomonas aeruginosa . Methods: The study included nine children (9-18 years) with CF, who contributed with 16 pairs of sputa collected before and after intravenous antibiotic courses: mass sequencing was performed of variable region 4 of the 16S rDNA gene, and total bacterial load plus selected specific pathogens assessed using quantitative real-time PCR. Results: The effect of anti-pseudomonal antibiotics was observable as a profound decrease in the total 16S rDNA load ($p = 0.001$), as well as in a broad range of individual taxa including Staphylococcus aureus ($p = 0.03$) and streptococci (S.oralis, S. mitis, S. infantis) ($p = 0.003$). Species richness was higher in patients with less profound markers of inflammation. Improvements in forced expiratory volume (FEV1) were connected with an increase in Granulicatella sp. ($p=0.004$), whereas negative association was noted between the total bacterial load and white blood cell count ($p=0.007$). Conclusion: The data show that the lung microbiome in children with CF is rather plastic reacting promptly to treatment. Certain species may be associated with changes in clinical parameters.

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TARGET-SPECIFIC MODULATION OF COMPLEX GUT MICROBIOTA USING NOVEL DNA-BASED NANOPARTICLE THERAPEUTICS

WONG, Nichola (1); MAYER, Melinda (2); MCARTHUR, Michael (3); NARBAD, Arjan (2)

Presented by WONG, Nichola

1: Institute of Food Research

Procarta Biosystems, United Kingdom 2: Institute of Food Research, United Kingdom 3: Procarta Biosystems

University of East Anglia, United Kingdom

nichola.wong@ifr.ac.uk

The complex human gut microbiota harbours 100 trillions of bacteria that are critical to health 1 . Imbalances in the microbiota have been associated with conditions such as inflammatory bowel disease and metabolic disorder 2 . For the advancement of microbiome-targeting, exploration of technology that modulates the gut microbiota in a specific manner is essential. For bespoke -spectrum antimicrobial activity, Snare™ antimicrobials combine Transcription Factor Decoys (TFDs) with the proprietary delivery nanoparticles. The TFDs competitively inhibit transcription factors to block expression of genes that are critical for the microorganisms' survival 3 . Using a TFD against an essential E. coli sigma factor , Snare™ antimicrobials induced target-specific antimicrobial activity against E. coli in the in vitro human colon model, with minimal disruption to the rest of the gut microbiota. This serves as a proof-of-principle that TFD technology has the capability to selectively modulate the gut microbiota. The Snare™ antimicrobial can potentially be developed to target other members of the gut microbiota to improve health status.

Supported by BBSRC, Procarta Biosystems

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The role of the colon microbiota in the Mexican children obesity

MURUGESAN, Selvasankar (1); GARCíA-MENA, Jaime (1); PIZANO-ZáRATE, Luisa Maria (2); MAYA, Otoniel (1); GALVáN-RODRíGUEZ, Flor María (1); MIRANDA-BRITO, Carolina (1); ROMANO, Marta (1); PIñA-ESCOBEDO, Alberto (1); HOYO-VADILLO, Carlos (1)

Presented by MURUGESAN, Selvasankar

1: Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico 2: Instituto Nacional de Perinatología, Mexico

selva@cinvestav.mx

Background Obesity is epidemic in Mexico, and among several other factors, the colon microbiota which produces short chain fatty acids by fermentation of undigested carbohydrates, plays an important role. Changes in the colon microbial diversity of Mexican children may affect nutrient absorption and contribute to development of obesity. Method Normal-weight (n=81), overweight (n=29), and obese Mexican children (n=80) aged 9-11 were selected. V3-16S rDNA libraries were prepared from fecal DNA and high-throughput sequenced 1 . After QIIME analysis of data, metabolic profile was done using PICRUSt 2 . Results The bacterial genera Blautia spp, Faecalibacterium spp and Coprococcus spp were significantly increased in overweight and obese children. Principal component analysis revealed association of these bacteria with increased BMI and triglycerides in overweight and obese children. Functional profile prediction disclosed that fatty acids, and lipid biosynthesis functional genes were significantly more abundant in obese children. Three different enterotypes were identified associated to these changes. Conclusion We conclude that a particular colon microbiota imbalance with different enterotype patterns in overweight and obese children, increases fatty acid and lipid production. These changes are associated with the increase of BMI and triglycerides in overweight and obese children.

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Multi-Omics Analysis of Microbial and Microbiome Samples

MILLER, Sandrine

Presented by MILLER, Sandrine

MO BIO Laboratories, United States

smiller@mobio.com

Understanding the biology of microorganisms is contingent upon successful collection and integration of genomic, transcriptomic and proteomic data. To date, methods for extraction and purification of DNA, RNA, and protein have been most commonly implemented as separate protocols or as a single protocol for co-isolation of DNA and RNA only. In addition, the few existing methods that extract all three biomolecules were designed for eukaryotic samples and fall short of complete microbial lysis and biomolecule recovery. To address the need for a sample preparation method that can provide high quality DNA, total RNA, and protein from microbial samples, we have developed a robust extraction chemistry that enables sequential isolation of these molecules. Here we present data from this new method.

Impact of Enterobius vermicularis infection and mebendazole treatment on intestinal microbiota and host immune response

YANG, Chin-An (1); LIN, Chia-Li (1); HSIAO, Chiung-Tzu (1); LIANG, Chao (2); PENG, Ching-Tien (3); CHANG, Jan-Gowth (1)

Presented by YANG, Chin-An

1: China Medical University Hospital, Taiwan, Province of China 2: National Chiao Tung University, Taiwan, Province of China 3: Children's Hospital of China Medical University, Taiwan, Province of China

yangginan81@gmail.com

Objectives : Previous association studies on Enterobiasis and risk of developing chronic inflammatory diseases revealed contradictory results 1-3 . We aimed to investigate whether Enterobius infection could influence our intestinal immune response and shift the microbiota to a composition that is beneficial to the host. Methods: Stool specimens were collected from 109 school-aged children either infected or uninfected with Enterobius vermicularis . Fecal samples were collected again in 65 subjects 2 weeks after taking 100 mg mebendazol. Gut microbiome composition was measured via 16S rRNA-sequencing. Intestinal cytokine and sIgA levels were detected by ELISA. Results:

Enterobious exposure increased the intestinal microbial diversity. Mebendazole treatment further enriched the relative abundance of the probiotic bacteria Bifidobacterium longum and Streptococcus thermophilus . Moreover, pinworm infection significantly decreased intestinal sIgA levels, while the amounts of IL-1 ß and IL-4 remained unchanged. Of note, stool IL-4 was negatively associated with the abundance of Alistipes , which was found to be increased after Enterobius infection. Mebendazole increased sIgA level in subjects with higher proportions of gut Streptococcus and Collinsella after treatment. Conclusion: Childhood exposure to Enterobiasis and mebendazole could be beneficial in terms of enrichment of intestinal probiotic species. The impact of mebendazole treatment on sIgA restoration is dependent on host microbiome composition.

Supported by China Medical University Hospital

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