ERA-NET Cofund HDHL-INTIMIC: **Intestinal Microbiomics** *funded projects*

The main objective of the Cofunded call for research proposal on "Interrelation of the INtesTInal MICrobiome, Diet and Health" was gaining new insights on the gut microbiome and it's causal relation to health, the impact of dietary components and strategies for preventive and therapeutic applications.

This Joint Action funded 11 projects for a total amount of about 9.6 M€.

DiGuMet

Diet x gut microbiome-based metabotypes to determine cardiometabolic risk and tailor intervention strategies for improved health

WHAT

The gut microbiota has been linked with incidence and progression of non-communicable diseases and their risk factors. Moreover, diet has been identified as an important modulator of microbiota composition and function. The underlying mechanisms of diet - microbiota interactions remain to be elucidated to provide a foundation for tailored dietary strategies. The aim of the DiGuMet project is to investigate how gut microbiota interact with diet and to identify the role of these interactions on cardiometabolic risk factors.

WHO

The DiGuMet consortium consists of three funded partners from Sweden, Spain and Italy and two collaborators from Denmark and Italy.

HOW

In this project extensive metabotyping will be carried out using metagenomics and metabolomics combined with lifestyle data in a free-living prospective cohort subset. The hypothesis is that gut microbiota - diet interactions are a major determinant of the metabotypes and that distinct metabotypes could be reflected by predictive biomarkers. These could then be used to tailor personalised dietary interventions for subjects at elevated risk of cardiovascular diseases. The hypothesis will be tested in a dietary intervention rich in fermentable vs non-fermentable cereal fibres among subjects with signs of metabolic syndrome and with distinct differences in their microbiota and microbiota-derived metabolites patterns.

FUNDING

DiGuMet receives approximately 0.68M€.

Coordinator: Rikard Landberg (Charlmers University of Technology, Sweden)

DIME

The role of diet-dependent human microbiome encoded T3SS-dependent effectors in modulating health

WHAT

Proteobacteria respond strongly to dietary changes and have been proposed as a diagnostic marker of microbial dysbiosis. Proteobacteria have secretion systems by which the so-called 'effector-proteins' can be injected into

the host's cytosol to interact with host proteins and modulate molecular pathways. DIME will investigate how diet-responsive commensal gut microbes modulate health by injecting microbial proteins into human cells to affect regulation and metabolism.

WHO

The DIME consortium consists of three Partners from Germany, Austria and France.

HOW

DIME aims to analyze the protein-protein interaction network of effector proteins from commensal microbes with the human host interactome to understand which processes and disease modules are targeted by this molecular mechanism. First, effectors and secretion systems in microbial reference genomes and meta-genome datasets will be identified, especially those that change in response to certain diets. Open reading frames will be submitted to experimental and bioinformatic interaction mapping/prediction using high-quality pipelines. The resulting host-microbe interactome map will be used to identify targets, processes, and disease modules that are perturbed by microbial effectors. For selected examples the molecular mechanism will be elucidated. The project results may enable dietary or pharmaceutical interventions based on specific interference or secretion-blocking strategies.

FUNDING

DIME receives approximately 0.72M€.

Coordinator: Pascal Falter-Braun (Helmholtz Zentrum München, Germany)

Di-Mi-Liv

Dietary modulation of intestinal microbiota as trigger of liver health: role of bile acids

WHAT

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. Alterations of gut microbiota composition and associated impairments of intestinal barrier function are critical in the onset and progression of NAFLD. Bile acids and microbial bile acid metabolism may play a pivotal role as mediators of gut-liver-crosstalk affecting NAFLD initiation and progression. Soluble fibers bind bile acids and modulate intestinal microbiota composition and may thereby affect metabolic parameters and liver health. Manipulating gut microbiota composition through prebiotics may improve NAFLD progression. However, the molecular mechanisms remain incompletely understood and established therapeutic strategies are missing.

WHO

The Di-Mi-Liv consortium consists of five funded partners from Austria (2), Germany (2) and Sweden and two collaborators from Germany,

HOW

Di-Mi-Liv combines the expertise of five groups with strong backgrounds in various aspects of diet, liver disease, bile acids and gut microbiota. Using clinical interventions with mouse models, the project aims to determine whether the interaction of bile acids and intestinal microbiota is critical for NAFLD initiation and progression. Furthermore, the project addresses whether diet and more specifically prebiotics can target this liver disease, thereby improving disease progression and overall health.

FUNDING

Di-Mi-Liv receives approximately 0.86 M€.

Coordinator: Ina Bergheim (University of Vienna, Austria)

earlyFOOD

Long-term impact of gestational and early-life dietary habits on infant gut immunity and disease risk

WHAT

Man is colonized immediately upon birth by microbes of primarily maternal origin. Initial

colonization and transfer of maternal immunity through breastfeeding are believed to impact infant health by conferring protection from infection and potentially resistance to metabolic and allergic diseases. This project assesses the importance of dietary habits on maternal immunity and on neonatal colonization and installation of immunological tolerance by a novel high-throughput immune-metagenomic approach.

WHO

The earlyFOOD consortium consists of five partners from France (2), The Netherlands, Spain and Italy.

HOW

EarlyFOOD will integrate immuno-metagenomics, metabolomics and toxicological as well as epidemiological data, such as exposure to dietary-derived metabolites and pollutants as well as infectious events, antibiotics, allergens and air pollutants in a birth cohort of individuals living across Europe in environments of different biodiversity. The impact of gestational and early-life dietary habits on microbiota dysbiosis will be identified by biostatistical modelling of metabolic and allergic disease risk as well as neurobehavioral disorders. The program will identify predictive biomarkers and early-life preventive strategies for the growing epidemic of human metabolic and allergic diseases with important impacts on public health and socio-economic benefits.

FUNDING

earlyFOOD receives approximately 1.1M€.

Coordinator: Martin Larsen (Cimi-Paris, France)

FATMAL

Identification of the molecular interplay between dietary fatty acids and gut microbiota in NAFLD

WHAT

Obesity promotes Non Alcoholic Fatty Liver Diseases (NAFLD) through mechanisms involving the gut microbiota. Cohorts of obese individuals (FLORINASH project), in which a multilevel omics approach was used, allowed us to identify a specific microbiome architecture indicating novel molecular hypotheses to be validated. In other cohorts, transcriptomic analyses from intestinal biopsies and 16S sequencing of liver samples suggested: 1. impaired intestinal defense favoring translocation of bacteria towards the liver, inflammation and lipid deposition and 2. impaired intestinal and liver lipid metabolism. The interaction between dietary lipids and the gut microbiota in the etiology of NAFLD is unknown and could impair intestinal defense and lipid handling.

WHO

The FATMAL consortium consists of four Partners from France (2), Sweden and Italy.

HOW

Using original and complementary models of genetically modified mice and germ-free mice colonized with human microbiota, FATMAL will study the impact of different lipid-enriched diets on: 1. gut microbiota and its causal role in liver disease; 2. intestinal immune- and non-immune defense systems; 3. translocation of bacteria towards the liver responsible for inflammation; 4. lipid handling processes in the liver and the intestine and 5. gender aspects by studying the role of the estrogen receptor α (ERα) in the gut microbiota/dietary lipids interplay.

FUNDING

FATMAL receives app. 0.96M€.

Coordinator: Rémy Burcelin (Inserm, France)

GUTMOM

Maternal obesity and cognitive dysfunction in the offspring: cause-effect role of the GUT MicrobiOMe and early dietary prevention

WHAT

Early life is fundamental for brain and microbiota development as gut microbiota influences brain function. Maternal obesity affects maturation of gut microbiota and is an important predictor of cognitive dysfunction in the

offspring. Cognitive decline through life is an increasingly invalidating condition, due to population ageing and the high frequency of predisposing factors (obesity, unhealthy diets). GUTMOM hypothesizes that the negative effects of maternal obesity on cognitive function in the offspring are partly mediated by the microbiota and its metabolites, offering the opportunity for non-invasive risk-screening and -reduction by tailored foods and diets, since earliest life stages.

WHO

The GUTMOM consortium consists of four funded partners from Italy, The Netherlands, Germany and Spain and three collaborators from Italy, The Netherlands and Finland.

HOW

GUTMOM will use two existing children cohorts to identify the gut bacteria and metabolites that are related to maternal obesity and offspring's cognitive development in early, pre-scholar and scholar age. Animal models will be used to investigate cause-effect mechanisms, and develop tailored dietary interventions to counteract the effects of maternal obesity on the gut microbiota, improving offspring's cognition.

FUNDING

GUTMOM receives approximately 0.79€.

Coordinator: Patricia Iozzo (Consiglio Nazionale delle Ricerche, Italy)

MeaTIc

Faecal Microbiome as determinant of the effect of diet on colorectal cancer risk: comparison of meat based versus pesco-vegetarian diets

WHAT

Colorectal cancer (CRC) is strongly affected by diet, with red and processed meat increasing the risk.

WHO

The MeaTIc consortium consists of five partners from Italy (2), France (2) and The Netherlands.

HOW

To understand the role of the microbiome in determining the effect of diet, in particular red/processed meat intake, on CRC risk, MeaTic will study the gut microbiome profiles and CRC biomarkers of healthy volunteers. These will be fed for 3 months with: a high-CRC risk diet, a normalized CRC risk diet or a low-CRC risk diet and examined at the beginning and at the end of the intervention. To study colon carcinogenesis, the same diets will be fed to carcinogen-induced rats or to Pirc rats, mutated in Apc, the key gene in CRC. Faecal microbiome profiles will be correlated to carcinogenesis measuring preneoplastic lesions, colon tumors, and faecal and blood CRC biomarkers as in humans. Third, to further elucidate the underlying mechanisms, faeces from rats fed the experimental diets will be transplanted into carcinogen-induced germ-free rats, measuring how microbiome changes correlate with metabolome and disease outcomes.

FUNDING

MeaTIc receives approximately 0.8M€.

Coordinator: Carlotta de Filippo (National Research Council, Italy)

MEDIMACS

Impact of MEditerranean Diet, Inflammation and Microbiome on plaque vulnerability and microvascular dysfunction after an Acute Coronary Syndrome. A randomized, controlled, mechanistic clinical trial

WHAT:

Coronary atherosclerosis is a leading cause of mortality and disability worldwide. Efforts are needed to improve secondary prevention and understand the mechanism underlying disease progression. Based on primary prevention trials, a potential benefit of the Mediterranean diet after an acute coronary syndrome can be anticipated. The integrated microbiome-mediated/immunologic and metabolic pathways by which the Mediterranean diet modifies cardiovascular

risk remain mostly unknown. Intestinal and oral dysbiosis is involved in the pathogenesis of atherosclerosis and microbiome dynamics may account for some of the observed benefits of Mediterranean diet.

WHO

The MEDIMACS consortium consists of four partners from Spain, France, Israel and Sweden.

HOW

MEDIMACS aims to evaluate the effects of a Mediterranean diet intervention on atherosclerotic plaque vulnerability and coronary endothelial dysfunction after an episode of acute coronary syndrome. The second objective is to decipher the interplays among diet, microbiota, immunity and metabolism responsible for the observed effects. A randomized mechanistic clinical trial, using state-of-the-art efficacy read-outs is proposed. This study will provide valuable insights to identify potential microbiome therapeutic targets for coronary artery disease.

FUNDING

MEDIMACS receives approximately 0.77M €.

Coordinator: Francisco Fernández-Avilés (CIBER, Spain)

MICRODIET

Understand and prevent production of microbially-produced pro-diabetic metabolites in different ethnic group: impact of dietary change

WHAT

Metabolic disorders such as obesity and type 2 diabetes (T2D) represent a growing clinical need. Accumulating evidence shows that the collection of human intestinal microbes influence host metabolism. Diet is one of the most important factors shaping the gut microbiome. So far, mainly microbial metabolism of dietary fibers has been studied, with less emphasis on proteins.

WHO

The MICRODIET consortium consists of three partners from Sweden, France and The Netherlands.

HOW

In this project it will be investigated how metagenome data available from different ethnicities are associated with different dietary patterns and how they respond to diets high and low in proteins. Second, bioreactors will be used to investigate how microbiomes from patients/healthy controls respond to high/low protein diets as well as aromatic amino acids with the hypothesis that the microbiome produces bioactive compounds. One metabolite, imidazole propionate (ImP) from histidine has been identified to be increased in blood of subjects with prediabetes and T2D and can directly impair insulin sensitivity. It will be investigated whether a low-protein diet (thus low in histidine) improves metabolism, alters the microbiota and reduces diabetogenic metabolites in T2D patients of different ethnicities. Finally, it will be confirmed if the microbiome produces ImP in humans using isotope-labelled histidine.

FUNDING

MICRODIET receives approximately 1.0M€.

Coordinator: Fredrik Bäckhed (University of Gothenburg, Sweden)

OCTOPUS

A sound microbiota in a sound body through apolipoprotein A-I and HDL: from mouse models to humans

WHAT

ApoA-I/HDL has been recognized to exert a beneficial role in cholesterol homeostasis and immunity, and to be anti-atherogenic.

JPI a healthy diet for a healthy life

The OCTOPUS project aims to demonstrate that apoA-I/HDL can also modulate intestinal homeostasis and microbiota composition and notably, that an apoA-I/HDL deficiency-driven dysbiosis can predispose to atherosclerosis development.

WHO

The OCTOPUS consortium consists of four partners from Italy, Germany (2) and France.

HOW

The OCTOPUS project originates from preliminary data indicating that i) apoA-I deficient mice have an altered microbiota composition, enriched in choline-degrading bacteria; ii) gut microbiota can influence atherosclerosis development by metabolizing dietary choline. In this study it will be assessed to what extent different levels of apoA-I/HDL modulate gut microbiota composition, intestinal homeostasis/immunity, host metabolome and atherosclerosis development in atherosclerosis-prone, dyslipidemic mouse models and in two large human cohorts (PLIC, LURIC). In addition, microbiota from mice and humans with different levels of apoA-I/HDL will be transplanted in atherosclerosis-prone germ-free mice to mechanistically assess to what extent low apoA-I/HDL levels make the gut microbiota harmful for atherosclerosis development. The results obtained will potentially shed light on an aspect of apoA-I/HDL biology that has not been investigated before.

FUNDING

OCTOPUS receives approximately 1.0M€.

Coordinator: Giulia Chiesa (Università degli Studi di Milano, Italy)

The HDHL INTIMIC has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement n. 727565

TransMic

The transition from a traditional to a Western lifestyle and its effect on the interrelation between diet, gut microbiome and health

WHAT

Chronic diseases have increased to epidemic proportions in Western countries. The composition of the gut microbiota influences health and disease. The comprehensive systems biology approach of the Human Functional Genomics Project (HFGP) offers unprecedented opportunities to unravel these effects. Still, important gaps in our knowledge remain of how diet influences the microbiome composition and its effects on health. TransMic aims to fill these gaps by studying the effects of traditional versus modern 'Western' diets on gut microbiome and the functional consequences for health.

WHO

The TransMic consortium consists of three funded partners from The Netherlands, Germany and Italy and one collaborator from Tanzania.

HOW

Cohort data from populations in different phases of the demographic transition from Tanzania, Burkina Faso and Europe will be analyzed using the comprehensive HFGP approach. In addition, a short dietary intervention will be performed switching young subjects from a Western to a traditional diet and vice versa. Omics-based data, including microbiome composition, genetics, transcriptome and lipidome will be related to functional data, such as immune responses. This large-scale analysis will provide fundamental insights in the effects of diet on microbiomeand health in general and effects of 'westernization' of diet in particular. It will thereby provide the necessary data for future innovative interventions to improve health, such as directed dietary microbiota modulation.

FUNDING

TransMic receives app. 0.82 M€.

Coordinator: Mihai Netea and Quirijn de Mast (Radboud University Medical Center, the Netherlands)