Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

HDHL-INTIMIC
Call for Joint Transnational Research Proposals on "INterrelation of the IntesTInal MICrobiome, Diet and Health"

A sound microbiota in a sound body through apolipoprotein A-I and HDL: from mouse models to humans (The OCTOPUS Consortium)

Graciela Delgado [a], Winfried März [a,b,c], Marcus E. Kleber [a], Marco Busnelli [d], Philippe Gérard [e], Olivia Gräbner [f], Giulia Chiesa [d]

[a]Medical Clinic V, Mannheim Medical Faculty, Heidelberg University, Mannheim, Germany, [b] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria,[c]Synlab Academy, Synlab Holding Deutschland GmbH, Mannheim, Germany, [d] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milano, Italy; [e] INRA, France; [f] Metabolomic Discoveries GmbH, Potsdam, Germany

BACKGROUND

Cardiovascular disease (CVD) remains the leading cause of death and morbidity worldwide. High density lipoprotein (HDL) has been shown to exert a broad spectrum of anti-atherogenic effects able of halting or even reversing atherosclerosis in several animal models (**Fig. 1**). This effect has been demonstrated when apolipoprotein A-I (apoA-I), the most abundant protein of HDL, was transgenically overexpressed or exogenously administered. Low levels of apoA-I/HDL are a common finding in several inflammatory and immune diseases in addition to atherosclerosis suggesting a potential link between apoA-I/HDL and immunity. Moreover, accumulating evidence supports the idea that besides its role in reverse cholesterol transport apoA-I/HDL is a component of the innate immune system, the first line of defense against invading microorganisms. The small intestine plays a fundamental role in lipoprotein metabolism and, together with the liver, is the major organ responsible for the synthesis of apoA-I that, besides being a protein component of HDL, is also present in chylomicrons.

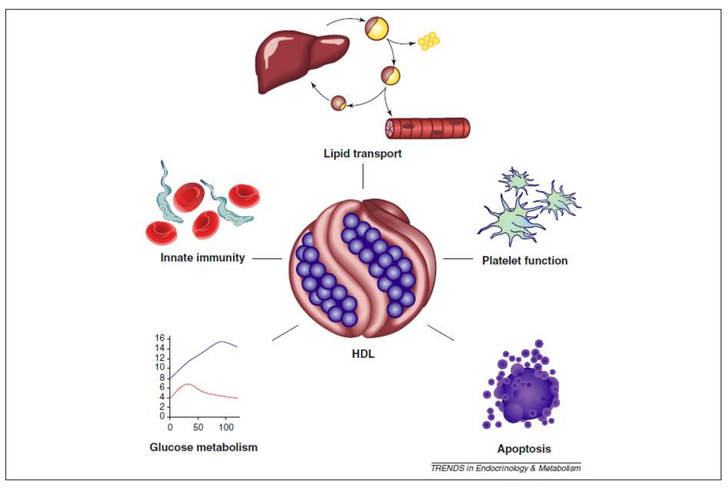

Fig. 1: The increasing functional heterogeneity of high density lipoprotein. [Gordon et al., Trends Endocrinol Metab. 2011 Jan;22(1):9-15]

The intestine plays not only a pivotal role in dietary lipids metabolism, but it also represents the largest compartment of the immune system and it is continuously exposed to a wide range of antigens and potential immune stimuli. Notably, the intestine harbours trillions of microbes that belong to all three domains of life. Nowadays, it is widely recognized that the content of the intestine, such as dietary constituents and commensal bacteria, influences physiological and pathological processes throughout the body. The gut microbiome also contributes to a substantial proportion of the variation in blood lipids (**Fig. 2**).
Importantly, alterations in the distribution of the species that make up the intestinal microbiota (dysbiosis) can induce increased permeability of the intestine, leading to increased systemic levels of bacterial products and predisposing to a variety of different diseases, including inflammatory bowel disease, colon cancer, gastric ulcers, non-alcoholic fatty liver disease, obesity, metabolic syndrome, these latter associated with cardiovascular disease risk.

The microbiota of mice lacking apoA-I has a different community structure compared with that of wild-type mice, characterized by a reduction of barrier-protective bacterial species (Bifidobacterium spp.) and an increase of endotoxin-producing species belonging to the phylum Proteobacteria (Desulfovibrionaceae) [Zhang et al., ISME J. 2010 Feb;4(2):232-41]. Preliminary results in atherosclerosis-prone (apolipoprotein E-deficient, EKO) mice, lacking or overexpressing apoA-I, and thus characterized, respectively, by extremely low or very high HDL levels, highlighted a number of differently expressed genes between the two mouse lines, of which some could be related to host-microbiota interaction.

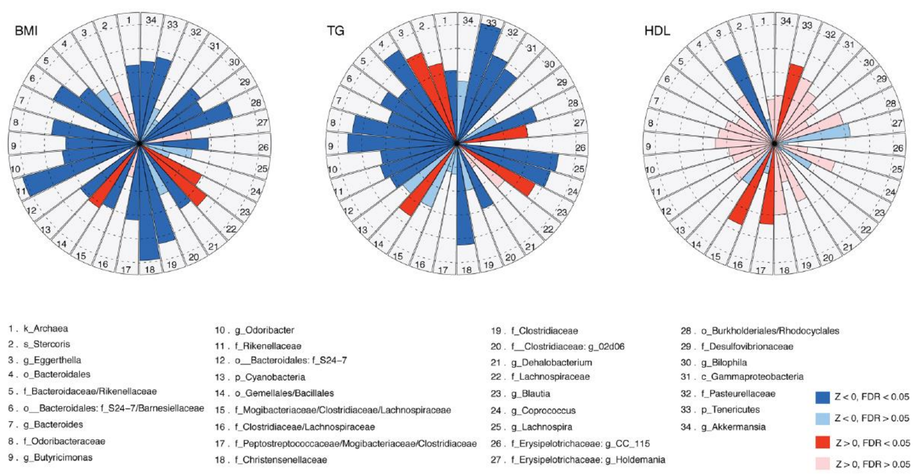

Fig. 2. The effect of taxonomies on body mass index (BMI) and lipids. The effects of 34 taxonomies associated with BMI, triglycerides (TG), and high-density lipoprotein (HDL) are shown as Z scores. Red sectors indicate positive associations and blue negative associations. Brighter colors indicate that the association was significant at false discovery rate (FDR) 0.05 level. [Fu et al., Circ Res. 2015 Oct 9;117(9):817-24]

AIMS

OCTOPUS aims to demonstrate for the first time, 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. The multidisciplinary and transnational consortium will assess 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 [Progressione della Lesione Intimale Carotidea (PLIC), Ludwigshafen Risk and Cardiovascular Health study (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 open a completely new scenario and shed light on an aspect of apoA-I/HDL biology never investigated before.

OCTOPUS is formed by four partners from three European countries (**Table 1**). The specific objectives of the project are summarized in **table 2** and the work plan is structured in four work packages (**Fig. 3**).

Table 1: Partners of the OCTOPUS consortium

Partner	Institution, Department	Type	Country
Coordinator	Department of Pharmacological and Biomolecular Sciences, UNIVERSITÀ DEGLI STUDI DI MILANO	Academia	Italy
1	INRA, Micalis Institute, AgroParisTech, Université Paris-Saclay	Academia	France
2	V Dept. of Medicine, Medical Faculty Mannheim, Heidelberg University	Academia	Germany
3	Metabolomic Discoveries GmbH, Potsdam	SME	Germany

Table 2: Specific objectives of OCTOPUS

Obj. No.	Description
1	To determine, in genetically modified mouse models, to what extent different levels of apoAI/ HDL modulate gut microbiota composition, intestinal homeostasis/immunity, plasma metabolome and atherosclerosis development.
2	To determine whether apoA-I/HDL levels can modulate gut microbiota composition and plasma metabolome in human cohorts. Possible correlations between microbiota composition and metabolic parameters will be evaluated.
3	To conduct SNPs analyses to highlight polymorphisms in genes involved in the microbiota-host cross-talk which could influence apoA-I/HDL levels.
4	To mechanistically assess to what extent low apoA-I/HDL levels make the gut microbiota harmful for atherosclerosis development.
5	To disseminate to the general public, scientific community, and stakeholders the scientific questions, aims, initiatives and results of the project.

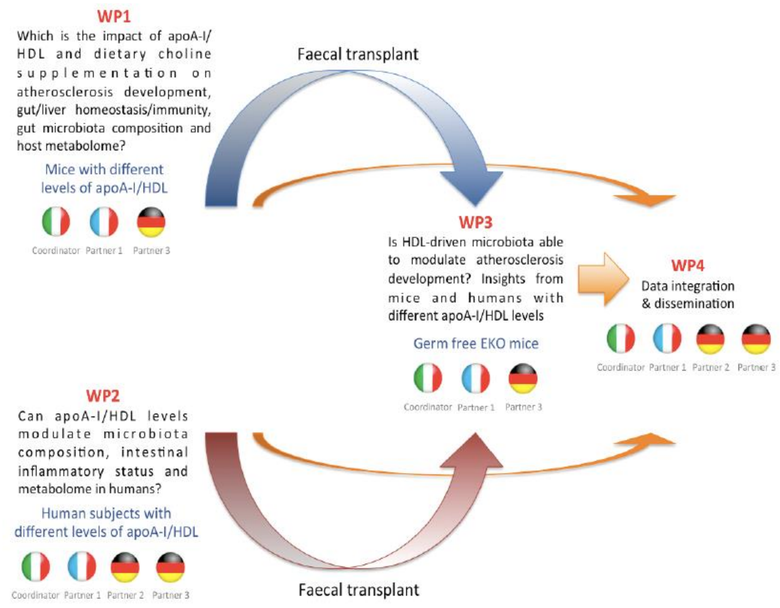

Fig. 3: The four work packages and the interrelation between them.

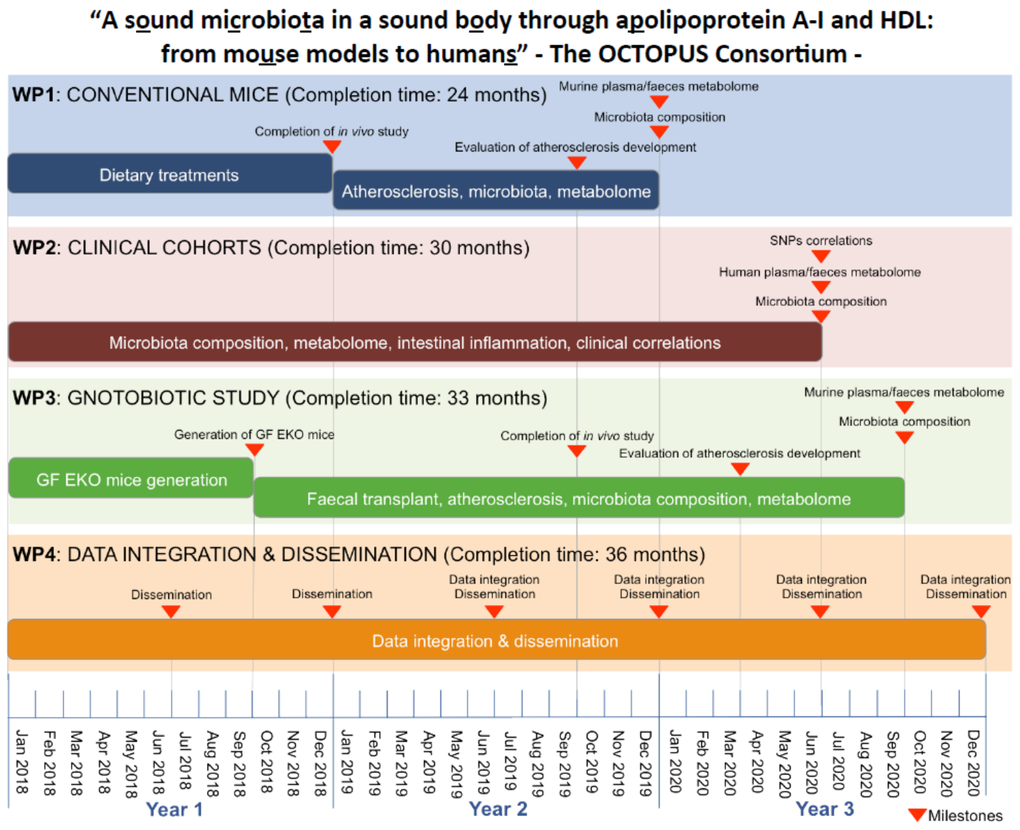

Fig. 4: GANTT chart of the OCTOPUS project with milestones indicated (official start of the project was delayed until November 2018).

•Graciela Delgado, Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany; Fon: +49 (0621 383-5172; Graciela.delgado@medma.uni-heidelberg.de