

PhD Project Advertisement

Project title: Odd-Chain Fatty Acids and Gut Bacterial Metabolites in Cardiac Metabolic Remodelling: Implication in the Therapeutic Strategy of Cardiovascular Disease

Project No: FBS2024-012-Su-qr

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Project description:

Intensive research has focused on the health beneficial effects of unsaturated fatty acids and adverse effects of saturated fat on cardiovascular disease (CVD). Both of unsaturated and saturated fatty acids are even-chain fatty acids, which represent the majority of the total fatty acids in our food. However, there is also a sub-group of fatty acids, the odd-chain fatty acids (OCFAs), which have been shown to play an important role in human health. Cardiometabolic analysis revealed the inverse association of plasma OCFA concentrations with the risk of CVD. It is generally assumed that OCFAs are totally derived from dietary consumption of milk and other dairy products that are originated from bio-synthesis in rumen microbiome. However, this assumption has been challenged by the evidence that shows the ratio of C15:0 to C17:0 in human plasma is approximately 1:2, which is opposite to the ratio of 2:1 detected in dairy fat. This evidence implicates the existence of other endogenous metabolic pathways for OCFAs.

Previously, research from my team and other scientists have demonstrated that increased colonization of a gut bacteria, *Akkermansia muciniphila* (*A. muciniphila*), in host gut can prevent high-fat-diet induced obesity, hyperlipidaemia, and insulin resistance in human and animal models. Increased plasma level of Trimethylamine N-oxide (TMAO) is associated with high risk of CVD. It has been known that the precursor of TMAO, trimethylamine (TMA) is exclusively produced by gut microbiome using dietary components, including carnitine and choline as substrates. We further found that *A. muciniphila* regulates plasma metabolomics profile by inhibiting production of TMA and TMAO, which may implicate the potential cardio-protective effect of *A. muciniphila*. Recently, two newly-discovered bacterial trimethylamines, 3-methyl-4-(trimethylammonio)-butanoate (3M-4-TMAB) and 4-(trimethylammonio)-pentanoate (4-TMAP) that are

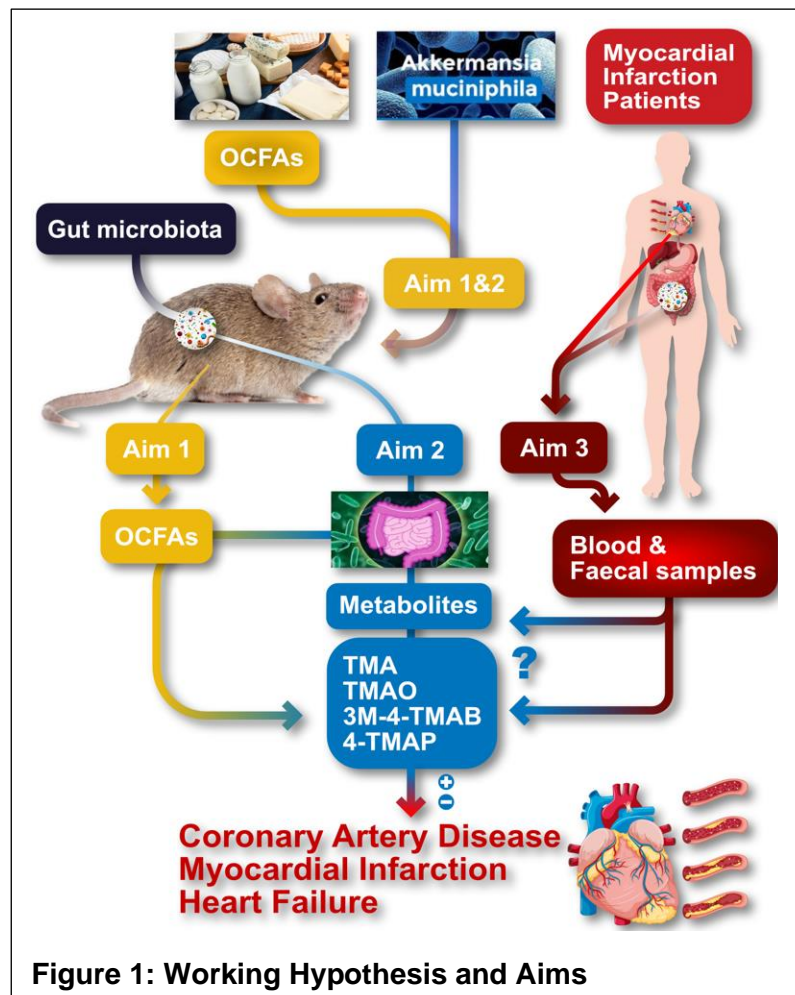


Figure 1: Working Hypothesis and Aims

structural analogs of carnitine, were found exclusively accumulated in the heart and brain tissues. However, their roles in CVD is not fully understood. Therefore, **the overarching goal of this project** is to delineate the mechanistic links between *A. muciniphila*, OCFa metabolism and the gut bacterial metabolites (including TMA, TMAO, 3M-4-TMAB and 4-TMAP) and their roles in coronary artery disease (CAD). This project will pursue **three specific aims** outlined below and in **Figure-1**.

Aim-1: Determine the impact of high OCFa diet on the metabolism of TMA, TMAO, 3M-4-TMAB and 4-TMAP and their association with the onset of CAD and the associated myocardial infarction (Figure-1). This project will utilize a mouse model of apolipoprotein E^{-/-} and SR-BI^{-/-} double knockout (DKO), which spontaneously developed multiple MIs and cardiac dysfunction in a pathological path similar to human atherosclerosis. This will enhance the translational potential of research findings from this project.

Aim-2: Investigate the regulation of *A. muciniphila* on OCFa metabolism and gut bacterial metabolites TMA, TMAO, 3M-4-TMAB and 4-TMAP (Figure-1). We will increase the colonization of *A. muciniphila* in mouse intestine via oral gavage of *A. muciniphila*, and determine plasma and cardiac concentration of TMA, 3M-4-TMAB and 4-TMAP by metabolomics profiling and desorption electrospray ionization (DESI) mass spectrometry. We will further investigate whether *A. muciniphila* and OCFAs synergistically prevent the development of CAD by improving mitochondrial function and endoplasmic reticulum stress.

Aim-3: Define the association between *A. muciniphila*, OCFAs, and the bacterial metabolites, TMA, TMAO, 3M-4-TMAB and 4-TMAP in humans (Figure-1). To determine the translational potential of our study, we will collect blood and faecal samples from healthy controls and myocardial infarction patients for analysing plasma concentrations of TMA, TMAO, 3M-4-TMAB, 4-TMAP, OCFAs C17:0 and C15:0, and the abundance of faecal *A. muciniphila*.

Successful delivery of this project will advance our knowledge on how dietary OCFAs modulate gut bacterial metabolites and host metabolism to prevent CVD. **Novel findings from this project may further lend support to the food industry for producing food products (i.e., dairy products) fortified with OCFAs, which will benefit the prevention and treatment of CVD.**

Training opportunities:

- The PhD programme will provide essential training on independent research ability, including project initiation, experimental designs, data interpretation and critical thinking.
- The proposed research will provide training opportunity to learn and utilize cutting-edge biomedical science research approaches across a wide range of life science disciplines, including human disease studies, animal model establishment, gut bacterial culture, Liquid chromatography–mass spectrometry, desorption electrospray ionization mass spectrometry, metabolomics profile analysis, and molecular and cellular biological techniques.
- The appointed student will be able to interact with ~150 postdoctoral fellows and postgraduate students in the School of Biological Science who are working on related research projects. As part of the PhD training program, the student will undertake the home office licenses training for a personal license to work with animal research and other lab skill training needed to perform the proposed research.
- The appointed student will be given the opportunity to present their research findings at international conferences, attending workshop and training programs during the PhD study. Therefore, successful completion of this PhD training program will equip the graduate with the necessary skills to enter the job market, drive progress in biomedical science and tackle global challenges in food, nutrition and human health.

Student profile:

Students with at least a BSc honours degree at upper second-class level (or equivalent) in Food Science, Biochemistry, Nutrition, Biomedical Sciences, Life Sciences or a closely related subject would be suitable for this project.

Stipend (Salary):

FoodBioSystems DTP students receive an annual tax free stipend (salary) that is paid in instalments throughout the year. For 2023/24 this is £18,622 and it will increase slightly each year at rate set by UKRI.

Equality Diversity and Inclusion:

The FoodBioSystems DTP is committed to equality, diversity and inclusion (EDI), to building a doctoral researcher(DR) and staff body that reflects the diversity of society, and to encourage applications from under-represented and disadvantaged groups. Our actions to promote diversity and inclusion are detailed on the [FoodBioSystems DTP website](#).

In accordance with UKRI guidelines, our studentships are offered on a part time basis in addition to full time registration. The minimum registration is 50% FT and the studentship end date will be extended to reflect the part-time registration.

For up to date information on funding eligibility, studentship rates and part time registration, please visit the [FoodBioSystems website](#).