

Application for 2 Scientia Fellows Postdocs

Title: Lifestyle-related disease: Dietary intervention studies and biomarkers

Applicants: Kirsten B. Holven, Andrew Collins, Asim Duttaroy, Leiv Ose, Kjetil Retterstøl, Per Ole Iversen, Christine Henriksen and Rune Blomhoff; Department of Nutrition, IMB, University of Oslo

Economy: Confirmation of funding of one postdoc from host is enclosed (the enclosure describes funding for 3 postdocs, one of which is in the field of clinical nutrition, i.e this application). In addition, one of the applicants (Per Ole Iversen) applied for a postdoc in the 2014 postdoc call from IMB. This will also be used as host funding for Scientia Fellows postdoc. Thus, we apply for a total of 2 “incoming” Scientia Fellows postdocs.

Lifestyle-related diseases represent one of the world’s greatest health problems, and are the leading cause of death globally (WHO: Global status report on non-communicable diseases, 2010). Numerous dietary components have been identified as signaling molecules that can alter metabolism and gene functions, and thereby influence health.

The overall objective for the “cluster” is to perform dietary intervention studies with the aim to identify biomarkers of health and disease and to understand how dietary components exert their effects, related to the development of disease. The successful candidate will be associated to one of more of the following studies:

1. The Norwegian Dietary Guidelines and Colorectal Cancer Survival Study. PI: Professor Rune Blomhoff

This research project is part of a big project with several collaborators that is based on a large clinical intervention trial of colorectal cancer (CRC) patients. The major aim of the CRC trial is to investigate the long-term effects of an intensive dietary life-style intervention on survival and disease-free survival. The aim of this application is to obtain funding to investigate whether molecular patterns obtained through ‘omics’ technologies are related to dietary treatment effects. We have established a comprehensive biobank of samples collected in a consistent, precise manner. The ‘omics’ technologies (transcriptomics, proteomics, epigenomics, genomics) will be applied to study the molecular effects of the intervention, in targeted subgroups of the trial population, aiming at discovering molecular patterns that will be important for future prediction of response to dietary interventions in combination to medical therapies to optimize individualized treatment.

2. Antioxidant supplements in acute stroke: Functional and cognitive outcomes. PI: Professor Per Ole Iversen

A growing number of elderly suffers from stroke. This puts an increase of resource-demand on the society and will lead to debilitating consequences for the patients. In stroke brain cells are damaged, partly due to accumulation of oxygen-derived substances - oxidants. Whether supplements with antioxidants can reduce the brain damage by inhibiting the oxidative stress after acute stroke, is unknown. In collaboration with several stroke-units as well as national and international scholars, we will perform a randomized, double-blinded placebo-controlled intervention trial to examine the effect of an antioxidant-rich juice on acute ischemic stroke. We will primarily test if supplementation of an antioxidant-rich juice given immediately after the onset of acute ischemic stroke will improve the physical and/or cognitive capacity among the patients.

3. Effect of low carbohydrate high fat diet in healthy non-obese adults, a randomized study. PI: Professor Kjetil Retterstøl

In this project we will explore the large differences between individuals in the response of a low carbohydrate high fat diet (LCHF). We have observed this phenomenon in clinical practice and thereafter confirmed it in two small pilot studies, of which one is now published. Our working hypothesis is that the great variation in the physiological response may be due to genetic differences and therefore genotype and gene expression will be studied in relation to the biochemical and physiological responses to LCHF diet. Our aim is to understand *how* saturated fat affects the key risk factors for cardiovascular disease at a molecular level. The relation between saturated fat and low density lipoprotein (LDL-cholesterol) is well known at the aggregate level. However, less is known about the

large individual differences observed in our pilot studies. The present project will use LCHF diet as a model to provoke a response in gene expression and biomarkers. Use of LCHF diet leads to large changes in human physiology and thus represents an excellent possibility for studies at a molecular level for improved understanding of lipid metabolism, important for understanding atherosclerosis, the major cause of cardiovascular disease (CVD).

4. **Compliance to dietary interventions PI: Associate Professor Christine Henriksen**
In this project we will study how patients adherence to dietary interventions, and the factors contributing to different compliance among patients. We will study factors related to the clinical nutritionist, to the patient (e.g. motivation), the communication style (e.g. use of motivation techniques), the setting and frequency of follow up. New techniques for measure of compliance and follow-up via computer- and smartphone based apps will be studied. Different hypothesis will be tested in the three patient groups involved in the above-mentioned studies (cancer, stroke and coronary heart diseases).
5. **Biomarkers of genome (in)stability: PI Professor Andrew Collins.** ComNet' is a network of researchers who use the comet assay in human biomonitoring. We are compiling a comprehensive database of human population studies employing the comet assay: more than 50 research groups worldwide have agreed to provide data. A pooled analysis of collected data will be carried out to determine basic parameters relating to DNA damage in humans. One aim of the ComNet project is to reduce the current level of inter-laboratory variation, and to establish the comet assay as an authoritative, validated biomonitoring assay. Standard protocols will be devised, and tested using 'ring studies'; guidelines for using the assay will be published. The comet assay (single cell gel electrophoresis) is the method of choice for measuring DNA damage in human cells.
6. **Investigations of anti-hypertensive and cardio-protective effects of fruits in humans PI: Professor Asim Duttaroy.** Acute and chronic cardiovascular events may result from alterations in the activity of the renin-angiotensin aldosterone system and activation of the coagulation cascade and of platelets. Medications that inhibit angiotensin converting enzyme (ACE) are widely prescribed in the treatment and prevention of cardiovascular disease. Platelets from such patients show spontaneous aggregation and an increased sensitivity to agonists which results in vascular damage and endothelial dysfunction associated with CVD. The project will be related to identifying the anti-platelet and anti-ACE compounds in fruits and to test the ability of these food derived compounds to decrease the formation of blood clots (thrombi) and lowering blood pressure in human volunteers.
7. **The interplay between diet, LDL-cholesterol and inflammation in children with familial hypercholesterolemia. PI: Professor Kirsten B Holven**
CVD caused by atherosclerosis is the main cause of mortality in Norway. Mild hypercholesterolemia is primarily lifestyle-induced, but more severe hypercholesterolemia is often caused by a genetic disposition such as familial hypercholesterolemia (FH). Few studies have elucidated the inflammatory component of CVD in susceptible subjects. Untreated FH children are hence unique in order to investigate these early pathological mechanisms of atherosclerosis since the high LDL cholesterol in these children is caused by a mutation while high LDL cholesterol in adults may serve as a marker of unhealthy life style, confounding the relation between LDL cholesterol and inflammation. Together with drug therapy, all FH patients are advised to follow certain lifestyle recommendations. However, although this dietary modification has known benefits in the commonly occurring non-FH hypercholesterolemia in adults, the clinical effects of such intervention in children with FH are largely unknown.

Scientific relevance.

Due to the widespread nature of lifestyle diseases, the identification of food derived compounds that exhibit a beneficial effect will have strong clinical potential. We aim to identify early biomarkers, which are related to the development of disease. Early biomarkers can assist in identifying individuals at high risk in early stages of disease, and identification of nutrient-related biomarkers may contribute to increase the importance of dietary modulation for the prevention of disease.