Samenvatting toegekende LSH-PPS projecten 2022

LSHM202201: Federated data driven decision support for Crohn's disease

Public summary

The FRESH project aims to predict treatment response of Crohn's disease (CD) patients to certain treatments by using artificial intelligence (AI) in order to aid in CD treatment decision making. Unique about this project is the strong 7-partner collaboration which includes 3 private parties, namely Janssen-Cilag, Patient+ and Sananet.
The FRESH project is a critical improvement on the current CD trajectory by reducing the need for trial and error in finding the right drug for a specific person. This current trajectory is not only problematic for patients as they experience symptoms of CD until the right drug is found, but also results in high health-care costs. This AI tool will be included in a decision aid for CD patients that also provides relevant information about their disease and possible treatments.
The project is particularly innovative in the way it builds this prediction of treatment response. In order to make a good prediction of a patient's future response to a treatment, it is crucial to gather large quantities of data from many hospitals. However, due to patient privacy this is often difficult or even impossible. The FRESH project solves this hurdle by employing the Personal Health Train, which allows our project members to use AI on data from many hospitals while retaining patient privacy.
Our end-product will be a prototype of a personalized decision aid for CD patients. This decision aid will contain an AI tool that predicts an individual's response to several treatment options. It will also contain relevant information about CD and these treatment options. These combined aspects of the personalized decision aid will subsequently be tested in a clinical study to determine whether the addition of this decision aid in clinical practice improves outcomes like patient satisfaction and decisional regret.

Consortium partners

- MUMC+: https://www.mumc.nl/themes/custom/mumc_base/assets/images/logo-maastricht-umc.svg
- Radboud UMC: https://www.radboudumc.nl/assets/img/logo/radboud/logo-nl-nl.svg
- Universitair Medisch Centrum Groningen (UMCG): https://www.umcg.nl/o/umcg-website-theme/images/desktop-umcg-logo.webp
- Janssen-Cilag: https://www.janssen.com/netherlands/sites/all/themes/janssen/logo.png
- SanaNet: https://www.sananet.nl/wp-content/uploads/2019/05/Logo_met_druppel-300x56.jpg
- Patient+: https://sp-ao.shortpixel.ai/client/to_auto,q_glossy,ret_img/https://patientplus.info/wp-content/uploads/2018/11/Patientplus_logo_rgb.png

LSHM202204: Collagen digestion and amino acid absorption kinetics *in vivo* in humans

Public summary

Collagen protein is the central structural component of connective tissue within muscle, bone, cartilage and skin. Connective tissue proteins have an important functional role in providing tissue elasticity. For skeletal muscle in particular, connective tissues transmit force generated from the contractile elements in muscle fibers via tendons and ligaments to the bone(s). These connective tissue protein networks are in a constant state of remodelling, mainly regulated by connective protein synthesis rates. Dietary protein ingestion is a major anabolic stimulus and has been well-established to stimulate muscle protein synthesis. Dairy protein is considered the preferred protein source to maximize myofibrillar protein synthesis rates. However, dairy protein contains insufficient glycine and proline to support an increase in connective protein synthesis rates. In contrast, collagen is rich in glycine and proline and has, therefore, been proposed as the preferred protein source to support connective tissue remodelling and, as such, to improve muscle and skin health. However, the digestion and absorption kinetics of collagen peptides and the impact on connective protein synthesis rates in muscle and skin has never been assessed *in vivo* in humans. In this collaborative project between UM and PB Leiner, we will first

produce intrinsically-labelled collagen peptides. For this a cow will be infused with stables isotopes, after which skin and bones will be collected to produce collagen peptides for human consumption. Next, we will apply these intrinsically labelled collagen peptides to quantify collagen peptide digestion and amino acid absorption and connective protein synthesis rates in muscle and skin in humans. Using stable isotope methodology, this project will generate fundamental knowledge on the bioavailability and anabolic properties of collagen peptide ingestion to support muscle and skin conditioning. This work has great relevance in the areas of 'health' and 'sports nutrition', and will open up new scientific and business opportunities.

Consortium partners

- Maastricht University
- PB Leiner

LSHM202205: 'Rapid molecular detection of sepsis from blood' Acronym: RaDos

Public summary

In this project we will study the dynamics of bacterial DNA during sepsis. Next to fundamental new insights into the presence and changes of bacterial DNA compared to microbiological culture and clinical illness, the diagnostic possibilities will be studied. In this project we will make use of total bacterial DNA analysis in whole blood from patients suspected for sepsis in time. The final goal will be to obtain more understanding of sepsis and treatment on a molecular level and improvement of therapy and reduction of morbidity and mortality. Based on the new fundamental molecular insights a new rapid (<6hr) complete molecular microbiological test for diagnosis of sepsis will be developed. Rapid diagnosis of sepsis is crucial for treatment and survival of patients with sepsis. Current tests take up to 48hrs-5days. This lead to unnecessary or antimicrobial over- or under-treatment which is associated with increased antimicrobial resistance development and high mortality rates. Early diagnosis of sepsis will have a major impact on the adequate treatment and reduction of mortality rates.
The social and economic impact is large because sepsis is one of the most important causes of death in hospitals. Sepsis is an expensive illness. Not only during stay at the IC department but also after recovery. Healthy people who survive from sepsis suffer from the consequences of the sepsis and need additional help. With a rapid diagnosis and adequate therapy this can be circumvented which saves money and give the patients a healthier live after sepsis.
A new public private partnership between University Maastricht/MUMC+, inBiome bv and Philips bv has been started. After the project a rapid new molecular method should be ready for production and implementation in clinical care. Subsequent implementation of this new approach in patient care will lead to optimization treatment, thus preventing development and spread of antimicrobial resistance and reduction of mortality and morbidity due to sepsis.

Consortium partners

- Maastricht University/Maastricht UMC+
- Philips bv
- inBiome bv

LSHM202206: Boosting the Bone Biology

Public summary

This project focusses on the treatment of large bone defects by using new techniques to improve the outcome. Novel materials from private partners who produce 3D printed implants (Osteopore, Singapore) and bioactive peptides for stimulation of bone growth (Cerapedics, USA) are investigated in clinical and laboratory studies.
Patients who are confronted with bone defects suffer from a dramatic decrease in health-related quality of life (QoL), which is even lower than the QoL reported by patients with colorectal or lung cancer. Treatment

success is limited by biological capacity and persistent infection which is present in up to 50 % of cases. These limitations result in multiple complex operations and long-term disability.
Treatment of large defects is multimodal, including cells, bioactive peptides and bone substitute materials. The ideal combination to support bone regeneration, however, is unknown. Moreover, containment of materials in large defects is problematic. The introduction of two novel technologies holds the promise to improve the outcome significantly; a 3D printed cage made of PCL, and a bioactive peptide. In a clinical study and in laboratory studies the effects of these materials on bone healing, bacterial growth and cell behavior will be studied in detail.
This project will describe the effects of these materials on treatment of 20 patients, including the cost-effectiveness. In addition, effects on bacterial growth, infection and cell growth are studied with different combinations of the mentioned materials. Increased knowledge and, if applicable, new cage compositions, will all be deliverables of this project.

Consortium partners

- Maastricht University, research institute NUTRIM/ MUMC+
- Maastricht University, MERLN Institute for Technology-Inspired Regenerative Medicine
- Cerapedics Inc.
- Osteopore International Pte Ltd

LSHM202211: Is fat a driver of Alzheimer's disease?

Public summary

Obesity is a risk factor for Alzheimer's disease (AD), which leads to cognitive decline and reduced quality of life. By 2040, AD will pose the highest disease-burden in the Netherlands, showing an urgent need for cognition‐improving treatments and risk stratification. Pinpointing the mechanisms of obesity-associated AD is crucial. Obesity induces adipose tissue (AT)-inflammation. Our data show that in an animal model of AD, the AT contains immune cells that are also present in the AD brain. We also showed that immune cells in AT mediate inter-organ crosstalk to promote disease, and that dietary intervention improves cognition. Whether AT-brain crosstalk via immune cells occurs in the context of AD in obese individuals, is unknown. Answering this knowledge gap is essential to develop long-awaited biomarkers for risk stratification, and novel therapeutics for this ever-growing condition. We hypothesize that the immune cell mediated AT-brain axis causes brain inflammation in obese individuals, thereby promoting cognitive decline, and development of AD. With assistance of Sciomics and Deeplife we will perform in-depth analyses of immune cells in blood and AT of obese and lean individuals to identify an obesity‐specific AT-signature. Cohorts undergoing weight interventions are assessed for correlations between immune cells and changes in BMI and cognition. This establishes mediators of the AT-brain axis promoting cognitive decline, providing valuable leads for new biomarkers and therapeutics. In parallel, animal studies will provide causal evidence of the involvement of the identified AT-signature in cognitive decline in AD-like mice. This new mouse model serves as a preclinical model to evaluate leads found from human studies, of which the selection will be done with Treeway and Medace. AT-BRAIN identifies new therapeutic targets for cognitive decline and develops novel biomarkers for obesity-linked risk for AD development. The consortium partners benefit from this project for development of their services, and use identified leads to further them into clinical trials.

Consortium partners

- Maastricht University – Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS) and Department of Internal Medicine, School for Cardiovascular Diseases (CARIM)
- Hasselt University – Biomedical Research Institute
- Treeway B.V.
- Deeplife
- Sciomics GmbH
- Medace B.V.

LSHM202212: **Discovering biomarkers for a degenerative eye disease**

Public summary

Fuchs endothelial corneal dystrophy (FECD) is a common degenerative eye disease and the only treatment for preventing blindness is corneal transplantation. In our project, we aim to discover a biomarker signature of FECD that can be detected in the patient's aqueous humour and develop a disease model that can be used to better understand this complex disease. This collaborative project brings together MUMC+ and Emendo, an exciting biotechnology company, dedicated to developing gene editing therapies for diverse diseases.

FECD affects 5% of the Dutch population and its typical age of onset is in the fifth or sixth decades of life, with most patients in Europe undergoing corneal transplantation in their seventies. In fact, due to ageing of the population, repeated corneal transplantation for FECD has become the second leading indication for corneal transplantation in Europe, further aggravating donor shortage. Our approach has the potential to identify persons at risk of developing or progressing disease, who are expected to benefit from therapeutic intervention with novel drug compounds. Success with this approach will limit the need for corneal transplants and chronic immunosuppression.

Aqueous humour is an accessible eye fluid in close contact with the corneal endothelial cells with a composition reflecting pathological processes. We will explore human aqueous humour as a source of molecular biomarkers for FECD. We plan to use high resolution mass spectrometry techniques to identify proteins in the aqueous humour that are present differently in individuals with and without FECD. In parallel we will also develop an in vitro disease model will be based on induced pluripotent stem cells generated from patients with FECD that are subsequently differentiated into corneal endothelial cells. This models give the possibility to test the effect of the medication on disease pathology and biomarker candidates.

Biomarker candidates that meet predefined selection criteria can be further developed into biomarker assays fit for implementation as (secondary) outcome measures in clinical trials using both the CRISPR based editing of Emendo or other companies working on gene editing for FECD. A disease model for FECD can be used to test future therapeutics and better understand this complex disease. Our approach may help to identify new biomarkers relevant for degenerative changes on the cellular level and support development of new precision medicines.

Consortium partners

- Emendo Bio
- Maastricht university
- MUMC+