Project 1

DEVELOPMENT OF A METHOD FOR HR MAS MRS ANALYSIS OF 13C-CHOLINE METABOLISM IN BREAST CANCER XENOGRAFT MODELS

We are currently studying two different breast cancer xenograft models and have found interesting differences in choline metabolism. Using 13C-labeled choline, these differences can be further explored. A student could establish a dosing regimen for 13C-choline and/or optimalize HR MAS MRS protocols for analysis of choline metabolism. The aim of the project is to be able to trace choline metabolism and to evaluate how choline metabolism changes following drug treatment.

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Project 2

QUANTITATIVE ASSESSMENT OF METABOLITES IN BREAST CANCER TISSUE, EVALUATION OF THREE ANALYTICAL TECHNOLOGIES

Background:
One in every ten women will experience breast cancer in her lifetime (Cancer Registry of Norway 2008). Breast cancer biology remains poorly understood and prediction of treatment response is highly inadequate. MR-derived metabolic profiles of breast cancer tissue have shown biomarker potential, classifying breast cancers according to clinical assessments and predicting patient long-term survival. To determine the transfer value to clinical application, biomarker candidates need to be critically evaluated for how they were discovered, including the experimental design, technologies and data analysis methods used. This project will provide a critical evaluation of MR-derived biomarker candidates for breast cancer. Three different analytical methods will be applied; solid state MRS (HR MAS), quantitative GC-MS (QQQ-GC-MS/MS) and high-resolution MRS. The extraction method of choice is expected to influence degree of extraction of different metabolites, and three different extraction methods will also be compared.

Aim:
To compare metabolite concentrations obtained by three different analytical methods from the same tissue specimen and evaluate the reliability of concentrations determined in intact tissue samples.

Methods:
The project will make use of tissue samples from an existing biobank administered by The MR Cancer Group, ISB, DMF (approved by the Regional Committee for Medical Research Ethics in Norway). The tissue samples are excised during scheduled surgery for breast cancer and immediately stored in liquid nitrogen (-196°C).

Samples included will be from large breast tumor biopsies (N=10). Six different sections of each biopsy (N=10) will be analyzed by HR MAS. After sample cutting for HR MAS analysis, tissue will be “printed” on a glass slide for later staining and subsequent pathological evaluation of presence of cancer cells. HR MAS analysis will be performed on the 6 different sections from each patient biopsy. After HR MAS analysis, samples will be extracted by three different extraction methods, leading to two sample extracts per extraction method. The extracts will be divided for analysis by QQQ-GC-MS/MS and solution HR MRS. This experimental setup will ensure two parallel samples for each comparison of methods. The project can be modified with respect to duration of project work.

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Project 3

DISCRIMINATION OF GLEASON GRADES IN PROSTATE CANCER PATIENTS USING MR METABOLOMICS

Background:
Prostate cancer is the most frequent type of male cancer worldwide and in Norway, and one out of 8 men will be diagnosed with prostate cancer during their life time. Currently, there are no accurate clinical methods for discriminating deadly from harmless types of prostate cancer, leading to overtreatment, unnecessary surgical interventions, stress of living with prostate cancer diagnosis and huge expenses for society.

Aim:
Metabolomics is an important future approach to provide new biomarkers and to understand the underlying molecular mechanisms (pathways) for prostate cancer aggressivity (Gleason grade). This understanding is especially important to be able to discriminate deadly from harmless disease, and for improving clinical diagnostics, prognostics, risk assessments and therapeutic monitoring for prostate cancer.

Methods:
The project will make use of tissue samples from an existing biobank (approved by the Regional Committee for Medical Research Ethics in Norway). Biopsy collection has been organized by the MR Cancer group at St. Olavs University Hospital in Trondheim since 2007. The tissue samples are excised during surgery or through TRUS-guided biopsies, and immediately stored in liquid nitrogen (-196°C). Tissue samples from prostate cancer patients
will be analysed with ex vivo high-resolution magic angle spinning magnetic resonance spectroscopy (HR MAS MRS) and all tissue samples will be described with various histopathological measures after MR analysis.

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Project 4

SUB-CLASSIFICATION OF BREAST CANCER PATIENTS BASED ON METABOLIC PROFILING

Background:
The field of transcriptomics has had a huge impact on breast cancer research the last decades. One of the important findings has been the classification of breast cancer into five distinct subgroups based on gene expression profiles. The five subtypes, Luminal A, luminal B, basal-like, her2/ERBB2+ and normal-like, have been established and show significant differences in clinical outcome.

Aim:
The aim of this project is to establish the metabolic profiles of the 5 gene expression based subtypes. The transcriptional and metabolic profiling of the same sample will capture the genetic and metabolic picture simultaneously, and may reveal more refined subgroups of breast cancer based on molecular properties of the tumor. Such subgroups can provide better stratification of patients for more personalized treatment regimes. New metabolic and genetic interactions may be revealed.

Methods:
The project will make use of tissue samples from an existing biobank (Oslo II study). The tissue samples are excised as fast as possible during surgery and are stored at -80°C. One piece of the tissue sample will be analysed with ex vivo high-resolution magic angle spinning magnetic resonance spectroscopy (HR MAS MRS). The MR procedure keeps the analyzed tissue intact after analysis, and all tissue samples will be described with various histopathological measures after the MR analysis. A second piece of the tissue sample will be analysed by transcriptomics and classified in accordance to the five genetic subtypes. This project is performed in close collaboration with the group of Prof. Anne-Lise Børresen-Dale at Rikshospitalet University Hospital (Radiumhospitalet).

A short description of the term metabolomics:
Metabolomics is the study of all metabolites in an organism or system, with the purpose to understand the metabolic state. Compared to the more well-established ‘omics technologies – genomics, transcriptomics and proteomics - metabolomics is a relatively new and emerging field. HR MAS MRS is a non-destructive technique that can be used on intact biological tissue to establish a metabolic profile. The MR spectra consist of thousands of variables describing
the detected metabolites. Analysing the interactions between all detected metabolites, and defining subsets of biomarkers for the problem to be addressed is thus important. Multivariate analysis is an integrated part of most metabolomics studies. Unsupervised, supervised, linear and non-linear techniques will be applied. In-house software and MatLab/R will be used for these analyses.

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Project 5

METABOLIC PROFILING OF TRIPLE-NEGATIVE BREAST CANCERS

Background:
Triple-negative breast cancers (TNBC) are characterized by absence of estrogen and progesterone receptors (ER/PR) and lack of over-expression of human epidermal growth factor receptor 2 (HER2). TNBC are associated with poor prognosis, due to aggressive tumor phenotype(s), only partial response to chemotherapy and present lack of clinically established targeted therapies.

Aim:
The main aim of this study is to establish the metabolic profile of TNBC, and use this to explore the molecular mechanisms underlying the TNBC phenotypic heterogeneity compared to breast cancers with better prognoses. Such knowledge may lead to advances in the design of individualized strategies for treatment of TNBC patients.

Methods:
The project will make use of tissue samples from an existing biobank (approved by the Regional Committee for Medical Research Ethics in Norway). Biopsy collection has been organized by the MR Cancer group at St. Olavs University Hospital in Trondheim since 2000 (regional collaboration with hospitals in the Central Norway Regional Health Authority. The tissue samples are excised during the surgery and immediately stored in liquid nitrogen (-196°C). Tissue samples from TBNC patients will be analysed with ex vivo high-resolution magic angle spinning magnetic resonance spectroscopy (HR MAS MRS) and further compared to tissue from a matched group of breast cancer patients with better prognosis. The MR procedure keeps the analyzed tissue intact after analysis, and all tissue samples will be described with various histopathological measures after the MR analysis.

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