

Mobility PhD fellowships
Reference no.: 2011-218/2-92

Graduate Programme no.: 4	Graduate Program name: Haematology
Theme: Individual prediction of efficacy and toxicity in cancer therapy and genomic analysis	Project title: Functional analysis of genes determining chemosensitivity by lentiviral transduction of B cells
Theme no.: GP4-T1	GP4-P1
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<p>Project description</p> <p>Every year approximately 2.500 Danes are diagnosed with B-cell derived blood-, bone marrow- or lymph node malignancies and receive chemotherapy attempting to eliminate the tumour. At present treatment strategies are based on characteristics of the individual diagnostic entities identified by clinical findings, histology, cytogenetics, immunophenotyping and molecular genetic data. However, very frequent patients suffer from disease recurrence demonstrating that individualized treatment guidance is required to improved chemotherapy responses and overall survival outcome.</p> <p>During the last few years much effort has been put into developing chemotherapy response predictors based on global gene expression profiles of tumours at time of diagnosis enabling an individualized treatment approach. These chemotherapy response predictors have been based either on <i>in vivo</i> class comparisons of clinical tumours from non-responders versus responders or <i>in vitro</i> based drug-response screening of disease relevant cell lines. Using the latter method we have generated gene lists of transcripts (both mRNA and microRNAs) with predictive power of melphalan sensitivity in Multiple Myeloma (Bøgsted M et al Generation of a predictive melphalan resistance index by drug screen of B-cell cancer cell lines. PLoS One. 2011 Apr 29;6(4):e19322) and R-CHOP sensitivity in Diffuse Large B cell Lymphoma (unpublished data).</p> <p>In order to validate experimentally the importance and role of the specific predicted genes and microRNAs with impact on chemotherapy sensitivity it is crucial to be able to transfect relevant cell lines so that their gene expression levels can be manipulated and their response to chemotherapy determined. Since B-cells are notorious difficult to transfect, a lentiviral vector transduction approach is applied to generate stable manipulated transcript expression (over- or under- expression of specific genes and microRNAs).</p> <p>The aims of this project are to:</p> <ol style="list-style-type: none"> 1) Objectively utilize bioinformatics to identify the strongest specific candidate mRNAs and microRNAs with impact on chemotherapy response; 2) Establish an optimized lentiviral vector system for delivery and stably expression of key mRNAs and miRNAs in B-cells; 3) Design and optimize systematic phenotypic assays that empirically can test the impact of candidate genes and microRNAs on chemotherapy response. <p>The position will be affiliated to the Research Laboratory of Department of Haematology, Aalborg Hospital, Aarhus University and the project will be carried out in close collaboration with the local and international physicians, statisticians, molecular biologists and genetics. Lentiviral transduction will be performed in collaboration with department of Human Genetics, Aarhus University.</p>	