Synopsis

Project title: Leukaemia and lymphoma diagnosis using nanotechnology

Background: Diagnosis and classification of acute leukaemias and lymphoproliferative syndromes (LPSs) is currently based on the evaluation of results from different and costly laboratory analyses. Alternative, highly precise, objective, less costly and less timeconsuming laboratory methods are urgently needed.

Recently, the company Nanostring Technologies has developed a new digital analysis system, the nCounter, which allows for precise gene expression profiling by direct counting of up to 800 individual mRNA molecules across all levels of biological expression. This system has become a well established technology in the Genomics Platform (CMU, Geneva), that appears ideally suited as an alternative to traditional microarray analysis, since it allows the analysis of

total RNA without a priori conversion into cDNA, the processing of crude cell lysates without RNA purification, and since it exhibits a very high sensitivity, specificity, and a high reproducibility.

Aims of the project: We plan to establish prediction algorithms for the diagnosis and classification of acute leukemias and of LPSs, using this new mRNA profiling system:

1. We will establish a classifier (= a set of genes) for Leukaemia diagnosis, in collaboration with the Munich Leukaemia Laboratory MLL, and T. Haferlach, an expert in the field of microarray analysis.

2. With the classifier we will analyse on the nCounter system 160 acute leukaemia samples from a previous study, for which we have already mRNA and the hematologic diagnosis at our disposal (= training set). Subsequently, we will analyse retrospectively 50 acute leukaemia

cases from Geneva. This experiment will show us the robustness of the classifier on our own samples obtained during routine hematologic work-ups (= test-set).

3. We will perform a prospective, multi-centre study of 300 acute leukaemia cases in collaboration with other centres in Switzerland (Bern, Sion, Lausanne, Aarau, Basel). With this study we will validate the classifier in a multi-centre setting and test its potential as a tool for prognosis determination. Survival data for each patient will be obtained.

4. In analogy to the leukemia classifier we will develop a classifier for the diagnosis of B cell LPSs. We will test the classifier on a set of 150 LPS cases, which have been extensively characterized by the Oncology, Hematology and Pathology Services of the Geneva Hospital, and for which we have tissue samples at our disposal (= training set). Then we will perform a validation study on 150 cases, which we will collect in the three-year study period (= test set).

5. We will use a new supervised learning approach based on fuzzy logic for the interpretation of the mRNA profiles (developed by one of us, Professor C. Pena). We will compare this approach to the conventional algorithms for cluster analysis and we will build predictive classification models, which will help us to reduce maximally the probe-sets used for sample analysis without loosing diagnostic precision.

The results of our study will define the potential of prediction algorithms for the diagnosis of acute leukaemias and B cell lymphomas, using the Nanostring technology as a new, rapid, sensitive and precise technology for mRNA profiling.

Time frame: 3 years

Requested budget: 2011: 141890.- CHF 2012: 144255.- CHF 2013: 149105.- CH