NCU – Summative report for 2013

Report submission date: 15.02.14

Principal investigator: Satu Mustjoki

Project title: *The Nordic CML study group: Immunological evaluation of factors related to the successful therapy discontinuation*

NCU grant received (€): 90 000

Project commencement and completion dates: 01.01.13 - project still continuing

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1. Briefly describe the project in a language understandable to non-scientists (max. 100 words)

The purpose of this project is to study how the immune system is able to control leukemia and prevent the expansion of leukemic cells. The study population consists of chronic myeloid leukemia patients who have achieved an excellent therapy response with current standard therapy (tyrosine kinase inhibitors, TKIs) and who are eligible for drug discontinuation. This study is related to clinical Euro-ski trial, which examines the probability to discontinue the TKI treatment without disease relapse. Both the clinical trial and immunological sub-study are ongoing in all Nordic countries and blood samples are collected from participating patients at the study entry, and at 1, 6, and 12 months after the TKI discontinuation.

2. Summarize the major findings of the project (max. 400 words)

The project has started in late fall 2012 and samples from first 60 patients have been collected with the help of NCU grant received for year 2013. Blood samples from participating Nordic centers (>10 different centers) have been sent to Helsinki, which is the core immunology laboratory in this study. Extensive cellular and functional immunological studies have been performed from fresh blood samples in order to find novel biomarkers, which could be used in the future to determine which patients are eligible for drug discontinuation.

Our preliminary results suggest that the NK-cell number and their function may predict disease relapse after TKI discontinuation. Interestingly, patients who were able to maintain remission had increased NK-cell counts already before stopping the treatment compared to patients who relapsed. Furthermore, the phenotype of NK-cells was more cytotoxic (CD57+CD16+CD62L-), and also their function (degranulation and direct cytotoxicity) was better in patients who did not relapse. No differences were observed in the function or the numbers of T-cells at the time of treatment discontinuation. However, the Th1 type of cytokine secretion by CD8+ T-

cells enhanced after the treatment discontinuation in patients who were able stay in remission. These findings may have impact on the future stopping trials. In addition, they further illustrate the importance of the immune system in the successful long-term treatment of CML.
Our plan is to collect additional 50 patients in order to understand the mechanism how NK-cells are able to keep the residual leukemia cells under control and prevent the disease relapse. When we understand the mechanisms of cure in a proportion of patients, we are able to devise treatment strategies, which will help the rest of the patients to achieve similar results. We believe that these principles are not specific for leukemia, but they may be directly applicable to other cancers as well.

3. Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (max. 150 words)

Recent evidence suggests that the immune system plays a major role in cancer. Many novel immunotargeting drugs are tested in cancer patients with promising results. Similarly, our results in CML suggest that the active immune system is crucial when we aim for the curative treatment outcome. Patients who were able to stop the anti-cancer treatment and stay in remission had higher amount of NK-cells and also the function of their NK-cells was better than in patients who relapsed after therapy discontinuation. We hope that when we understand the mechanisms of cure in a proportion of patients, we are able to devise treatment strategies, which will help the rest of the patients to achieve similar results. For example in the case of CML, we believe that the drugs which would activate the NK-cells could enhance the probability of cure. However, further studies are still needed to prove this hypothesis.

4. Outline how Nordic cooperation has added value to this project (max. 100 words)

Chronic myeloid leukemia is quite a rare cancer (incidence 1-2 patients/100 000) and hence clinical studies cannot be performed within one Nordic country. Therefore the Nordic CML study group (NCMLSG) was established in 2004 to be able to conduct high-quality academic clinical studies within the Nordic region. The current Euro-Ski study is an excellent example of this strong Nordic collaboration: both the number of patients included thus far in the clinical study (>80 Nordic patients out of 190 total patients) and in the immunological sub-study (60 patients) succeeds all other countries. With this Nordic framework we have been able to conduct top-quality research which has already now resulted in significant novel findings.

5. Publications resulting from the NCU research grant

Thus far the results have been presented with 2 abstracts, which have both been selected for oral presentations in international conferences:

1. ESH - iCMLf International Conference on CML - Biology and Therapy (September 26 - September 29, 2013 - Estoril, Portugal)

Title: Disease relapse after TKI discontinuation in CML is related both to low number and impaired function of NK-cells: Data from Euro-Ski

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2. 2013 American Society of Hematology (ASH) Annual meeting, (6-10 December, 2013, New Orleans, USA)

Title: DISEASE RELAPSE AFTER TKI DISCONTINUATION IN CML IS RELATED BOTH TO LOW NUMBER AND IMPAIRED FUNCTION OF NK-CELLS: DATA FROM EURO-SKI

Mette Ilander, Ulla Olsson-Strömberg, Hanna Lähteenmäki, Tiina Kasanen, Perttu Koskenvesa, Stina Söderlund, Martin Höglund, Berit Markevärn, Anders Själander, Kourosh Lotfi, Claes Malm, Anna Lubking, Marja Ekblom, Elena Holm, Mats Björeman, Sören Lehmann, Leif Stenke, Lotta Ohm, Hans Ehrencrona, Henrik Hjorth-Hansen, Susanne Saussele, Francois-Xavier Mahon, Kimmo Porkka, Johan Richter, Satu Mustjoki

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