NCU – Summative report for 2014

Report submission date: 150528

Principal investigator: Eva Hellström Lindberg

Project title: Nordic MDS Group (NMDSG) clinical trial program and new biobank and molecular platform to improve outcome for patients with MDS

NCU grant received (€): 50 000

Project commencement and completion dates:

140101 - 141231

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

MDS is blood cancer with overall poor prognosis but with considerable variation between patients. Known risk clinical scores in combination with the pattern of mutations is essential in order to provide the right advice and treatment for each individual patient. In this project the Nordic MDS Group has established a network of Nordic DNA biobanks and is analysing patients for mutations in 70 genes with known diagnostic and prognostic function. In addition, we are performing clinical therapeutic trials directed towards defined subgroups in order to further refine treatment recommendations for MDS.

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

1. *Patient cohorts.* We have decided to restrict analyses to population-based cohorts, since this is the main scientific strength of the project compared to other international cohorts.

2. *Molecular screen.* Major progress has been made in this part of the project. The Agilent Haloplex system with 72 genes has been evaluated and chosen for the analysis of >500 patients from Sweden, 200 from Denmark and 50 from Norway. In addition, 80 patients from Finland will be analysed with a similar panel. The panel have been validated in an already analysed cohort from Karolinska Institutet (KI). Coverage is excellent, 99%, with >2000-3000X sequencing depth. A firm algorithm pipeline has now been developed in collaboration with professor Richard Rosenquist, Uppsala, and in charge of the SciLife clinical sequencing platform (SC).

3. *74 gene panel.* APC, ASXL1, ATRX, BAP1, BCOR, BCORL1, BRAF, CBL, CEBPA, CREBBP, CSF3R, CTCF, CTNNA1, CUX1, DIS3, DNMT3A, ELANE, EP300, EPOR, ETV6, EZH2, FAM5C, FLT3, GATA1, GATA2, GATA3, GNAS, HNRNPK, IDH1, IDH2, IKZF1, IRF1, JAK2, JAK3, KDM6A, KIT, KRAS, LUC7L2, MLL, MPL, MYC, NF1, NOTCH1, NPM1, NRAS, NXF1, PDGFRB, PDS5B, PHF6, PRPF40B, PTEN, PTPN11, RAD21, RB1, RIT1, RPS14, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG1, STAG2, STAT5B, TET2, TP53, U2AF1, U2AF2, WT1, ZRSR2 + SNPs for del(5q) and del(7q).

4. Country-specific progress

5. Sweden: A biobank structure has been established based on the Swedish INCA registry and the bbmri.se at KI core facility. The process encompasses various quality control projects. Per 1 April 2015 the biobank had received 258 samples, >50% of all new patients. **300** samples will be sequenced within 2015. In addition, the KI biobank will submit 200 patient's samples prior to the start of the national biobank to the analysis.

6. Finland: The Finnish National biobank for hematology patients is already established including ethical permits and biobank and regional structure, as reported in the research program. Finnish samples will be analysed both using the Finnish panel and the Haloplex system. The SC has ensured that there is a complete overlap with the Haloplex screen, which will allow future quality control. MDS has before this NCU project not been in focus for research, but to date 42 MDS and 19 MDS-MPN = **80** patients have been sampled and will be analysed 2015. Finland has to this date analysed their samples and have been reimbursed from the NCU grant (SEK 91 298,00).

7. Denmark: DNA from a regional population-derived cohort from Copenhagen with complete clinical follow-up has been collected 2008-2011 and will be used for the project (n=39). A new cohort was initiated 2013. The ethical permit has been upgraded to include all newly diagnosed Danish MDS patients from June 2013. So far **95** Danish samples have been analysed and another **96** samples will be submitted during 2015. KI has sequenced these samples.

8. Norway: Norway has had a slower National development of National hematological cancer research biobanks. The SC therefore decided to use Bergen as a pilot area for collecting an academic regional population-based cohort. An ethical permit has been approved (2012/892/REK) and so far **50** consecutive patients have been biobanked and DNA have been isolated and analysed. KI has sequenced these samples.

9. Summary: **>650** samples obtained from population-based cohorts will be analysed during 2015. The selection of these patients will be compared with the local MDS cohort (n=approx. 300) at KI, with the clinical trial cohorts and with international cohorts. This is an internationally unique population-based cohort.

NMDSG Clinical trial program

In brief, the NMDSG10B for higher-risk MDS with del(5q) has opened in all countries and has recruited 60% of patients. NMDSG08A and 10A have been published during 2014. A novel study on chronic myelomonocytic leukemia (NMDSG14A) will open Q3 2015. All clinical trial patients are analysed by targeted sequencing.

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

Findings generated from the biobank projects have been included in large international datasets and publications. During this year, we will generate data allowing for comparison of our population-based databases with previously published more selected cohorts. Data from our and others publications will influence the new WHO 2015 classification. Two genes, SF3B1 as good prognostic marker and TP53 as bad prognostic marker will be recommended in the new diagnostic model based on our studies. The NMDSG10A study (phase I) has been taken forward to a corporate randomized phase III study. Azacytidine is based on NMDSG08A not recommended for lower-risk MDS. NMDSG10B aims to improve treatment for a dismal patient group, higher-risk MDS with del(5q).

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

MDS is a rare disease and these studies would not be possible without Nordic and International collaboration.

5. Publications resulting from the NCU research grant

Treppendahl MB, Qiu X, Søgaard A, Yang X, Nandrup-Bus C, Hother C, Andersen MK, Kjeldsen L, Möllgaard L, **Hellström-Lindberg E**, Jendholm J, Porse BT, Jones PA, Liang G, Grønbæk K. Allelic methylation levels of the noncoding VTRNA2-1 located on chromosome 5q31.1 predict outcome in AML. Blood. 2012;119(1):206-16.

Malcovati L, **Hellström-Lindberg E**, Bowen D, Adès L, Cermak J, Del Cañizo C, Della Porta MG, Fenaux P, Gattermann N, Germing U, Jansen JH, Mittelman M, Mufti G, Platzbecker U, Sanz GF, Selleslag D, Skov-Holm M, Stauder R, Symeonidis A, van de Loosdrecht AA, de Witte T, Cazzola M. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013 Oct 24;122(17):2943-64.

Tobiasson M, Dybedahl I, Skov Holm M, Karimi M, Brandefors L, Garelius H, Grövdal M, Høgh Dufva I, Grønbæk K, Jansson M, Marcher C, Nilsson L, Olsnes A, Porwit A, Saft L, Möllgård L, **Hellström-Lindberg E**. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor resistent, low and INT-1 risk MDS. Results from the Nordic NMDSG08A clinical Phase 2 trial. Blood Cancer J. 2014 Mar 7;4:e189.

Saft L, Karimi M, Ghaderi M, Matolscy A, Fenaux P, Mufti G, Giagounidis A, Selleslag D, Muus P, Sanz G, Mittelman M, Bowen D, Porwit A, Fu T, Backstrom J, MacBeth K, **Hellström-Lindberg E**. P53 Protein Expression is a strong predictor of outcome and cytogenetic response in patients with Low-/INT-1 risk myelodysplastic syndromes treated with Lenalidomide. Haematologica. 2014 Jun;99(6):1041-9.

Svensson T, Chowdhury O, Garelius H, Lorenz F, Saft L, Jacobsen SEJ, **Hellström-Lindberg E**, Cherif H. A pilot phase I dose finding safety study of the thrombopoietin-receptor agonist, eltrombopag, in patients with myelodysplastic syndrome treated with azacitidine. Eur J Haematol. 2014 Nov;93(5):439-45.

Karimi M, Nilsson C, Dimitriou M, Jansson M, Matsson H, Unneberg P, Lehmann S, Kere J, **Hellström-Lindberg E**. High-throughput mutational screening adds clinically important information in myelodysplastic syndromes and secondary or therapy-related acute myeloid leukemia. Haematologica. 2015 Mar 13. pii: haematol.2014.118034.

Malcovati L, Karimi M, Papaemmanuil E, Ambaglio I, Jädersten M, Jansson M, Elena C, Gallì A, Walldin G, Della Porta MG, Raaschou-Jensen K, Travaglino E, Kallenbach K, Pietra D, Ljungström V, Conte S, Boveri E, Invernizzi R, Rosenquist R, Campbell PJ, Cazzola M, **Hellström-Lindberg E.** SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood. 2015 May 8. pii: blood-2015-03-633537. [Epub ahead of print].