Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2014
Søknad	Nordic MDS Group (NMDSG) Clinical Trial program and new biobank and molecular platform to improve outcome for patients with MDS
Søknadsid	155289
Innsendt av	Eva Hellström Lindberg

Oppgave: Progress report

Tilordnet	Eva Hellström Lindberg
Status	Arkivert
Opprettet	04.02.2016

RAPPORT

Briefly describe the project in a language understandable to non-scientists

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.

Summarize the major findings of the project

Targeted sequencing of population-derived 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.

Molecular screen. Major progress has been made in this part of the project. The Agilent Haloplex system with 74 genes has been piloted and thereafter used to analyse three population-based cohort, in total 495 patients from Sweden, Denmark and Norway. NMDSG trials are not part of these cohorts. 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 Institute. Coverage is excellent, 99%, with >500X sequencing depth. A firm algorithm pipeline has been developed in collaboration with professor Richard Rosenquist, Uppsala, in charge of the SciLife clinical sequencing platform.

NMDSG clinical trials
NMDSG08A
Was finalised and published in 2015 (Tobiasson et al). Major finding that azacytidine is NOT an appropriate treatment for EPO refractory transfusion-dependent lower-risk MDS. Information has been included in the new version of the NMDSG guidelines for treatment of MDS.

NMDSG10B
A randomized phase II study allocating higher-risk MDS patients with a deletion of 5q to azacytidine vs azacytidine + lenalidomide. Plan: 72 randomized patients. Actual accrural: 60 randomized patients. Study will be closed at latest 31 Dec 2016.

NMDSG14B
A new study aiming for a fundamentally novel system for detection of minimal residual disease in MDS undergoing stem cell transplantation (SCT). Will be launched in Sweden April 2016 and in the other Nordic countries at latest Q4 2016. Planned first phase 200 patients over 24 months. The study concept uses deliverables from the molecular platform in the project to identify and then monitoring pre-SCT mutations post SCT.

Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer

Findings generated from the biobank projects have been included in large international datasets and publications. During this year, we have generated data allowing for comparison of our population-based databases with previously published more selected cohorts (first abstract will be submitted in 2 days). 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. Outcomes from the clinical trials, see above.

Outline how Nordic cooperation has added value to this project

MDS is a rare disease and these studies would not be possible without Nordic collaboration. Moreover we take advantage both of the good Nordic collaboration and the national register and biobank systems. In 2 years from now, our Nordic biobank and registers will have developed to a world-class resource.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
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	23980065
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	24608733
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 independently predicts outcome in patients with lower-risk myelodysplastic syndromes with del(5q). Haematologica. 2014 Jun;99(6):1041-9	24682512
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	24853277
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 Jun;100(6):e223-5	25769547
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;126(2):233-41	25957392
Tobiasson M, McLornan D, Karimi M, Dimitriou M, Jansson M, Ben Azenkoud A, Jädersten M, Lindberg G, Abdulkadir H, Kulasekararaj A, Ungerstedt J, Lennartsson A , Ekwall K, Mufti GJ, Hellström-Lindberg E Mutations in Histone Modulators are associated with prolonged survival during Azacitidine therapy. Accepted 2016-0222, Oncotarget	

Brief overview of expenditures for last year 1 vedlegg (NCU financial report 2015_Hellstrom-Lindberg.pdf)

NCU – Financial report for 2015

Report submission date: 160301

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:

150101 - 151231

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1. Brief overview of expenditures for 2015

Conference	45.916 SEK
Travel costs	2.783 SEK
Salary coordinator	92.933 SEK
Printing material/publications	8.423 SEK
Transfer to Denmark, Kirsten Grønbæk	100.000 SEK
Sequencing	148.356 SEK
Ethical application, NMDSG14B	16.000 SEK
Shipping charges	45.413 SEK
Rebuilding home page	29.600 SEK
Indi 20%	97.885 SEK
Total	587.309 SEK
Owing from 2014	89.579 SEK