NCU – Summative report for 2014

Report submission date:

Principal investigator: Göran Jönsson

Project title: Molecular epidemiology of familial ocular and cutaneous malignant melanoma; a Swedish-Danish collaboration

NCU grant received (€): 50,000€

Project commencement and completion dates:

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1. **Briefly describe the project in a language understandable to non-scientists (max. 100 words)**
   In current project we aim to investigate familial ocular and cutaneous melanoma which will lead to a better understanding of these diseases that are tightly linked but still different on a biological level. In familial cutaneous melanoma germline mutations in CDKN2A is a well established susceptibility gene. We are investigating tumor molecular properties from CDKN2A germline mutated patients with the aim of defining distinct features in such tumors. Familial ocular melanoma is rare and recently we and others have described inherited mutations in the BAP1 gene in ocular melanoma families. We are now aiming at investigating tumors from these individuals. In summary, we believe that tumor molecular information in tumors from familial melanoma may help to understand the development of the disease.

2. **Summarize the major findings of the project (max. 400 words)**
   Thus far, we have firmly established that BAP1 is an ocular melanoma susceptibility gene. In addition, we show that individuals with a BAP1 mutation also confer an increased risk to other cancers such as mesothelioma. In addition, we are involved in the search for cutaneous melanoma susceptibility genes and a study on this was recently published in *Journal of the National Cancer Institute*. We are currently performing targeted DNA sequencing of 100 ocular melanomas which will be compared to 100 cutaneous melanomas. The targeted gene panel includes all genes previously reported as mutated in melanoma. In a second project we have investigated the gene expression landscape of 43 cutaneous melanomas from CDKN2A mutation carriers. As a comparison we have gene expression data from 223 sporadic melanomas. Overall, no distinct difference was found between the familial and sporadic cases suggesting that the tumor

aberrations found in sporadic melanomas are similar to those found in familial melanoma. This study was previously published in *Journal of Investigative Dermatology*.

3. **Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (max. 150 words)**
   The project has increased our knowledge on how melanoma arises and in particular that BAP1 germline mutations confer risk of ocular melanoma and other cancer types. Furthermore, the project has increased our understanding with regards to tumor biology of familial cutaneous melanoma.

4. **Outline how Nordic cooperation has added value to this project (max. 100 words)**
   It has been very valuable with the Nordic Cooperation. In this way, it has been possible to examine a larger cohort of patients. We examine common and rare genetic forms of predisposition to cancer, and in this setting it is very valuable to be able to recruit material from large cohorts.
   The three collaborating research groups have different areas of expertise, which all three groups and the research have benefitted from.

5. **Publications resulting from the NCU research grant**

   A recurrent germline BAP1 mutation and extension of the BAP1 tumor predisposition spectrum to include basal cell carcinoma.
   Wadt KA, Aoude LG, Johansson P, Solinas A, Pritchard A, Crainic O, Andersen MT, Kiilgaard JF, Heegaard S, Sunde L, Federspiel B, Madore J, Thompson JF, McCarthy SW, Goodwin A, Tsao H, Jönsson G, Busam K, Gupta R, Trent JM, Gerdes AM, Brown KM, Scolyer RA, Hayward NK.
   Clin Genet. 2014 Sep 15

   Molecular characterization of melanoma cases in denmark suspected of genetic predisposition.
   Wadt KA, Aoude LG, Krogh L, Sunde L, Bojesen A, Grønskov K, Wartacz N, Ek J, Tolstrup-Andersen M, Klarskov-Andersen M, Borg Å, Heegaard S, Kiilgaard JF, Hansen TV, Klein K, Jönsson G, Drzewiecki KT, Dunø M, Hayward NK, Gerdes AM.
   PLoS One. 2015 Mar 24;10(3):e0122662

   Nonsense mutations in the shelterin complex genes ACD and TERF2IP in familial melanoma.
   Aoude LG, Pritchard AL, Robles-Espinoza CD, Wadt K, Harland M, Choi J, Gartside M, Quesada V, Johansson P, Palmer JM, Ramsay AJ, Zhang X, Jones

K, Symmons J, Holland EA, Schmid H, Bonazzi V, Woods S, Dutton-Regester K, Stark MS, Snowden H, van Doorn R, Montgomery GW, Martin NG, Keane TM, López-Otín C, Gerdes AM, Olsson H, Ingvar C, Borg A, Gruis NA, Trent JM, Jönsson G, Bishop DT, Mann GJ, Newton-Bishop JA, Brown KM, Adams DJ, Hayward NK.
J Natl Cancer Inst. 2014 Dec 13;107(2)

Primary melanoma tumors from CDKN2A mutation carriers do not belong to a distinct molecular subclass.
Staaf J, Harbst K, Lauss M, Ringnér M, Måsbäck A, Howlin J, Jirström K, Harland M, Zebary A, Palmer JM, Ingvar C, Olsson H, Newton-Bishop J, Hansson J, Hayward N, Gruis N, Jönsson G; Melanoma Genetics Consortium.
J Invest Dermatol. 2014 Dec;134(12):3000-3