SHORT TERM SCIENTIFIC MISSION (STSM) – SCIENTIFIC REPORT

The STSM applicant submits this report for approval to the STSM coordinator

Action number: BM1402
STSM title: Quantifying frailty in the PolG mouse model
STSM start and end date: 21/01/2018 to 26/01/2018
Grantee name: Ariane Scheuren

PURPOSE OF THE STSM/

Within the framework of my PhD project, I am currently evaluating the bone degradation and age-related osteoporotic phenotype in the PolG mouse model, which due to the expression of an exonuclease-deficient version of the mitochondrial DNA polymerase γ, exhibits accelerated ageing. Similar to the development of senile osteoporosis in humans, bone degeneration towards an osteoporotic phenotype in this model develops naturally with age (between approximately 20 and 40 weeks of age). In this respect, I am currently performing a pilot study, in which the 6th caudal vertebra of female homozygous and WT littermate controls are being monitored by *in vivo* micro-CT every 2 weeks between the age of 20 and 40 weeks. Once the exact time points of tissue degeneration to an osteoporotic phenotype have been determined, a second study is planned to investigate the effects of cyclic mechanical loading on osteoporotic bone in this model. The major advantage of the PolG model however, is that it develops multiple age-related phenotypes (including osteoporosis, hearing loss, greying hair, kyphosis and enlarged heart) early in life and thus, strongly mimics the multi-system morbidity observed during ageing in humans. Unfortunately though, our *in vivo* micro-CT approach is limited to the analysis of bone tissue, and hence, it will not provide sufficient information to evaluate the PolG mouse as a relevant model for the multi-organ ageing phenotype observed in humans. In this respect, frailty, defined as a clinical syndrome of accelerated ageing that manifests itself with the limited capacity to maintain tissue homeostasis and regeneration, is becoming more and more recognized in ageing research. Particularly, as frailty can also revert over time, it is thought that a better understanding of the underlying mechanisms could lead to the treatment or even prevention of the onset of age-related diseases. Indeed, the ageing phenotype in the PolG model has been shown to be reverted to wild type levels with exercise; however, the data of frailty measures in this model remains sparse.

With the above in mind, the aim of this STSM, which took place at the Mellanby Centre for Bone Research at the University of Sheffield, was to learn the techniques to assess frailty in mice according to the recently established mouse frailty index developed by Whitehead et al. As frailty can be assessed non-invasively and without the need of specialized equipment, these measurements could be incorporated into our longitudinal studies in which *in vivo* micro-CT is used to track bone degradation towards an osteoporotic phenotype in the PolG mouse model. Moreover, frailty measurements could also be included in a second study, which aims at investigating the effects of a previously established 4-week mechanical loading regime in the PolG model. However, as the assessment of frailty is intended to be a standardized tool in mouse

ageing research, the transfer of knowledge is extremely important to ensure reproducibility of the methods between separate laboratories.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

During my visit to the Mellanby Centre of Bone Research at the University of Sheffield, I have learnt the methods to score aged mice based on the mouse frailty index. A hands-on training session allowed me to learn the techniques required to measure and score each of the 31 parameters included in the scoring system. After the training session, the scoring was performed on a cohort (>20) of aged and young mice (male and female) and the results compared to those obtained by a researcher who is experienced in scoring aged mice using the frailty index (Samuel Hassan, PhD student under the supervision of Prof. Bellantuono). Furthermore, previously obtained frailty index data of young (age 12-15 weeks), middle-aged (age 34-43 weeks) and aged mice (age 82-95 weeks) was discussed in order to learn how the frailty index data can be analyzed and quantified.

In addition, I have learnt how to dissect hind-limb muscles from mice, which will not only allow me to perform histological analysis of muscle tissue, but also to send tissue samples to the group in Sheffield, if required (cf. section on future collaborations).

DESCRIPTION OF THE MAIN RESULTS OBTAINED

In line with the aim of this STSM, I have successfully learned how to score aged mice based on the mouse frailty index. The transfer of knowledge provided through this STSM thereby ensured reproducibility of the assessment of frailty between separate laboratories. Also, our animal facility at ETH Zurich currently does not have any aged mice in holding, and hence, this STSM allowed me to experience the appearance and behaviour of aged mice (up to 2 years of age).

Upon return to my home laboratory at ETH Zurich, I have started to score mice of the PolG strain (homozygous and wild-type littermates), which we are currently tracking using longitudinal *in vivo* micro-CT imaging in order to characterize the bone degradation towards an osteoporotic phenotype in this model. Furthermore, the combination of longitudinal *in vivo* micro-CT imaging with the frailty index measurements will allow a direct comparison of the results obtained by both methods and thus, help to determine the relevance of this imaging approach as a suitable tool in preclinical research on ageing.

Considering the benefits from the learned techniques, and furthermore, the enjoyment and profit from the interactions with the interdisciplinary group at the Mellanby Centre for Bone Research, I am convinced that the takeaways of this STSM will be extremely valuable to my career as a research scientist.

FUTURE COLLABORATIONS (if applicable)

As the group of Prof. Ilaria Bellantuono plans on using the PolG mouse model as well, we aim to collaborate with them by transferring our knowledge on the PolG model to their laboratory. As they are particularly interested in the development of sarcopenia in this model, we will – in addition to the frailty index measurements – start measuring the grip-strength longitudinally in a cohort of PolG mice in order to determine when skeletal muscle mass starts to decline. In contrast to the osteoporotic phenotype of the PolG model, the development of sarcopenia has been investigated quite extensively in previous studies, and hence, including the measurements of limb strength of these mice will allow a direct comparison to results

shown in literature. In line with this, I have also been taught how to dissect hind-limb muscles from mice, which will not only allow me to perform histological analysis of muscle tissue, but also to send tissue samples to the group in Sheffield, if required.

To my knowledge, the PolG mouse model has not yet been fully characterized according to the standardized protocols of the frailty index and hence, the acquired data would be valuable to other members of the MouseAGE COST Action, who are currently using, or planning to use this specific model.