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D 9.55 - Year 1 advisory panel report (Report)

Lead Author: Liz Ainsbury (DH-PHE)

With contributions from:

All project partners (HMGU, ENEA, DU, OBU) and Advisory Board members

Reviewer(s): CONCERT coordination team

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Abstract

The lens of the human eye is known to be more radiosensitive than previously thought but, despite a substantial reduction in occupational dose limits based on recent epidemiological information and reanalyses, the mechanisms of low dose radiation cataract induction are still unclear. This is an important current public health issue, for instance for medical radiation workers, many of whom will need to amend their working practices despite a clear understanding of the effects of chronic, low dose, ionising radiation exposure.

The LDLensRad project aims to bring together experts from across Europe to answer a number of key research questions on this topic, including: how does low dose radiation cause cataracts; is there a dose rate effect, and how does genetic background influence cataract development after radiation exposure. CONCERT Deliverable 9.51, 5.1.1 of the project, describes the detailed work plan and timing for irradiations of mice for long term and short term models of cataract initiation and development.

The experiments are currently being carried out in 6 different mouse strains, as described in the Gantt charts in Deliverable 9.51, to test the impact of genetic background and further inform the mechanistic understanding. Mice will be exposed to doses of 0 to 2 Gy at an acute, high dose rate (0.3 Gy/min) or at a more protracted, low dose rate (0.063 Gy/min), to assess the effect of dose protraction on the dose response for radiation cataractogenesis. Mice are being irradiated at 10 weeks (when they have fully developed lenses) at PHE and HMGU. At ENEA, mice are being irradiated at neonatal age (postnatal day 2), the age of peak susceptibility to radiation lens injury, and at 10 weeks, specifically in order to investigate the ageing effect in this particularly age-sensitive strain. The mice are then being followed for up to 18 mth post exposure, with Scheimpflug imaging taking place at 1 mth intervals to track the appearance and development of cataracts. Behavioural testing will be carried out concurrently and, at the end of the long term study, the lenses of surviving mice will be analysed for histological and morphological changes and the results compared with wider existing and newly collected data on wider systemic effects, to test the hypothesis that lens effects can be used as an indicator of global radiation effects.

In addition, for each strain, dose and dose rate, lenses extracted from groups of mice will be assessed for: initial DNA damage at 4 and 24 hrs following exposure; intracellular communication, cell cycle effects, biochemical analyses and genetic pathway analyses at 4 and 24 hrs, 4 and 12 mth; proliferative and morphological effects at 24 hrs, 4 and 12 mth; miRNA content using Next Generation Sequencing (NGS) at 4 hrs and qRT-PCR at 24 hrs, 4 and 12 mth, with appropriate sham irradiated controls for all endpoints. The results and associated analysis of these studies will be made available as further Deliverables as the project progresses.

This Deliverable summarises the input of the Advisory Board to the LDLensRad project during the first 12-months. AB members were present at both the Kick-off and month 10 progress meeting, and provided comments and advice both in person and in writing to the project members. This has clearly helped ensure the integrity and quality of the anticipated project outputs for Radiation Protection.

Content

1 Progress summary

The Advisory Board consists of 5 members from UK, US, Russia and Japan. In year 1, in addition to attending two meetings, the details of which are outlined below, the Advisory Board had ad hoc e-mail based discussions among members or with Research Partners, and also wrote to Research Partners to share the latest scientific information relevant to the project. In year 2, these activities will continue to ensure active involvement of the Advisory Board in order to support LDLensRad

2 Two day kick off meeting on month 5

Three of 5 Advisory Board members from UK, US and Japan were able to attend in person (two did not make it each due to a conflict in schedule and due to a visa-related issue). Over the first day and a half, they listened a series of presentations made by Research Partners and gave them specific comments. On the afternoon of day 2, the Advisory Board had a one hour closed meeting to prepare the report in which one more Advisory Board member was able to participate by telephone. This was followed by a 30 min presentation to deliver an Advisory Board report to Research Partners, where the Advisory Board raised various comments and suggestions, as summarized below.

In general, people are paying attention to LDLensRad. The project is well designed as a whole, but some improvements may strengthen and increase the merit of the project. The need for the project is well recognized, but the working hypothesis, the robustness of underpinning scientific evidence from the existing literature, and the expected scientific developments to be made by the project, may need to be considered in more detail in order to make the aspects clear to all partners. The biological significance of the new data to be obtained by the project is not completely/clearly explained so more clarity is also needed here - in particular regarding whether the working hypotheses and the endpoints under consideration have the potential to explain ionizing radiation cataractogenesis? It was also stressed that dosimetry must be validated and consistent at all facilities.

A number of additional, administrative, points were also discussed. Organization of the meeting: At the kick off meeting, 30 min were assigned to the Advisory Board session with no time for feedback from Research Partners. At the annual meetings in 2018 and 2019, it was suggested to have the Advisory Board session increased to 1 hour, so the Advisory Board may receive feedback from Research Partners to the comments and suggestions. The need for periodic progress reports was also discussed: concerns may be shared with the Advisory Board members on an ad hoc basis at any time, in addition to the annual face-to-face meetings.

Soon after the kick off meeting, a consensus on the content of the report was reached among all 5 Advisory Board members. The Advisory Board then submitted the report to Research Partners a week after the kick off meeting. Following discussion amongst the partners at European Radiological Protection Research Week, the Advisory Board received a written response from Research Partners, outlining how each of these points and further detailed comments on each WP will be addressed. In particular, further dosimetric validation will be carried out, and the scientific basis for the tasks under each WP will be discussed in more detail, in order to provide full justification for current practices or to propose the need for further amendments at the next annual meeting (scheduled for June 2018).

In addition, the Advisory Board shared thoughts with Research Partners, such as on the importance of the timeliness in terms of the report and publication, dosimetric protocols, in vitro doses, and on preparations of the abstracts, presentations and manuscripts.

3 Three hour progress meeting on month 10

Two of 5 Advisory Board members from Russia and Japan were able to attend in person. They listened to updates from Research Partners and gave them comments. On the same day, both also had discussions with the Research Partner on sampling and analysis of the lenses from Mayak workers.

4 Conclusions

Through attendance of Advisory Board members at face to face meetings or through regular email contact, the Advisory Board have had detailed input into the LDLensRad project to date, and it is anticipated that this will continue going forward. Further, there is clear evidence that the involvement of the Advisory Board will ensure the integrity and quality of the anticipated project outputs both in terms of understanding of mechanisms of radiation action in the lens and in support of more effective, evidence based, Radiation Protection of the lens in future years.