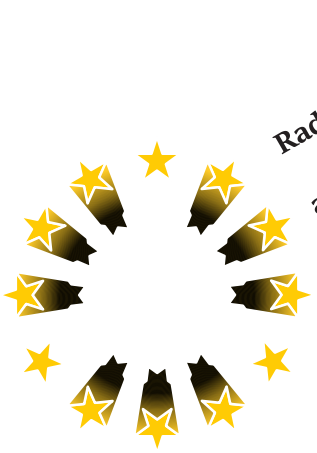

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PROJECT PROCARDIO: CARDIOVASCULAR RISK FROM EXPOSURE TO LOW-DOSE AND LOW-DOSE-RATE IONIZING RADIATION

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The study of cardiovascular effects is gaining greater impact amongst the radiation protection community following the publication of a number of epidemiological studies confirming an increased risk of cardiovascular disease at medium and high doses.

The PROCARDIO consortium challenged the hypothesis that there is no long-term health detriment resulting from damage to cardiovascular function exposed to low doses of ionizing radiation (below 100 mGy) To do this PROCARDIO established a consortium to create the first international platform for the study of radiation- induced cardiovascular disease after low-dose radiation exposure.

The PROCARDIO consortium consisted of 12 participating institutions based in eight different EU member states as well as one partner in Russia. The project dealt with investigating the link between cardiovascular disease and exposure of the heart and major vessels at lower doses to identify new biomarkers of radiation-induced cardiovascular disease.

Within the project cardiovascular dosimetry data was be collected from four cohorts of survivors of childhood cancer radiotherapy. Both animal and *in vitro* models were used to identify molecular biomarkers informing on the cardiovascular effects of low doses. Also radiation-induced non-targeted cell-cell interactions upon the heart were investigated. Mathematical models describing the biological mechanisms of radiation exposure were developed using both new and available epidemiological and animal data.

COGNITIVE AND CEREBROVASCULAR EFFECTS INDUCED BY LOW DOSE IONIZING RADIATION 'CEREBRAD' (GRANT AGREEMENT: 295552)

M.A. Benotmane

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Epidemiological evidences about the occurrence of late cognitive and cerebrovascular diseases due to exposure to radiation early in life (in utero or during childhood) are scarce. Nevertheless, A-bomb survivor data indicate a linear dose-response curve with a threshold around 200 mGy. Thus, raising the concern regarding the uncertainty of low-dose radiation, which is in part due to the lack of sufficiently large cohorts, combined with a lack of understanding the underlying mechanisms is very important. Moreover, the increasing use of radiation in medical diagnostics urges the need for appropriate research to define precisely the effect of low dose radiation on the brain. The FP7 CEREBRAD project for cognitive and cerebrovascular effects induced by low dose ionizing radiation (grant agreement n°295552), aimed to gather sufficient scientific evidence to increase the statistical power of epidemiological data. Thus, epidemiological evaluations of the risk of cerebrovascular disease following low dose exposures (Excess of Odds Ratio (EOR) of stroke per Gy of average radiation dose to the cerebral arteries, was equal to EOR/Gy = 0.49 (95% CI: 0.22 to 1.17)) based upon a cohort of survivors of childhood cancer receiving radiation therapy before the age of 5 year. While cognitive impairments have been evaluated in a medical and in 'in utero' exposed cohorts from Chernobyl, the project also aimed to explain the related cellular and molecular events modulated early after exposure which are most probably responsible for late cognitive and cerebrovascular diseases. The shape of the dose-response curve for cognitive impairments in animal models shows a linear dose-response curve with age-dependent sensitivity. In addition, when radiation is combined with other environmental toxicants, we believe there might be no threshold below which no effects are observed. Interestingly the cellular and molecular investigations revealed obvious effects of low-dose ionizing radiation 'LD-IR' on the brain at multiple levels. In general, we could observe a clear dose-dependent effect and could unveil different anomalies induced by the lowest X-ray dose studied (0.1 Gy) in terms of cognition, cell death and neurogenesis. Finally, mechanisms acting at low doses are different from those at high doses, while, processing of the late response could in part be mastered through epigenetic events, requiring thus additional future investigations.

A NEW ERA OF MOLECULAR EPIDEMIOLOGY REQUIRES BIOLOGICAL MARKERS: THE DARK MATTER OF THE GENOME EMERGES INTO THE LIGHT

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on behalf of the Dark.Risk* consortium

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In the late 1950s, public health initiatives in a number of countries mandated x-ray treatment for the depilation of the scalp as the standard of care for the treatment for children infected with the *Tinea capitis* fungal disease of the hair roots. This internationally standardized treatment protocol with radiation proved highly effective in combating the fungus. The standardized irradiation, narrow age-distribution and the possibility for long-term follow-up all suggests that these individuals would provide a powerful epidemiological approach to study the risks of low dose irradiation.

The strategy of Dark.Risk was to develop the Serbian Tinea Capitis Cohort (STCC) to provide epidemiological evidence for low dose radiation effects and determine if it was feasible to collect biological materials. At the same time the role of the non-coding RNA (ncRNA) "dark matter of the genome" was to be investigated to determine if this could provide valid candidate radiation biomarkers. The goal of the consortium was therefore to establish if ncRNA analysis would be feasible using biological materials obtained under field conditions from individuals of the STCC cohort.

We have produced a standard operating protocol (SOP) for the collection, storage and distribution of biological materials from the Serbian (STCC) cohort. These materials have proven acceptable for the analysis of non-coding RNA (ncRNA) levels in the circulation, opening the way for biomarker identification. In parallel studies we have established that both long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are regulated by radiation exposure, and that they influence a number of regulatory pathways, including metabolism, epigenetic markers, telomeric integrity and cell division. We have generated a database of responsive ncRNAs in cells from epithelial and neural tissues. The functioning of selected ncRNAs in radiation response has been studied in more details. These showed actions in epigenetic regulation of transcription, cell cycle control, and telomere stability, all processes important to a radiation response. Of particular note is that the response of one long ncRNA (PARTICLE) shows a clear non-linear dose response relationship. The non-coding microRNAs play a more limited role in cellular metabolism, regulating translation of coding mRNAs. These studies provide a new set of candidate biomarkers for identifying radiation responses.

*Supported by the EURATOM Radiation protection programme project Dark.Risk (Grant agreement n°: 323216).

RADIATION-INDUCED AGING AND GENETIC INSTABILITY OF MESENCHYMAL STEM CELLS: AN ISSUE FOR LATE HEALTH EFFECTS?

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Mesenchymal stem cells (MSCs) are a source of adult multipotent cells important in tissue regeneration.

The aim of this study is to analyse the interaction of non-physiological high oxygen and low-dose gamma-irradiation onto growth, senescence and DNA damage in murine MSC.

There has not been much interest in the past to study the response of adult stem cells such as MSCs to radiation exposure, probably because for connective tissue tumors (sarcomas, derived from mesenchymal cells) the radiation-associated excess relative risk (ERR) among the A-bomb survivors was much lower than for carcinoma or for leukaemia (Preston et al 2003). This picture looks much different, however, when patients irradiated with higher radiation doses for therapeutic purposes are studied: external beam radiotherapy confers a high risk for the induction of therapy-associated secondary tumours, in particular sarcomas derived from mesenchymal stem cells.

In this presentation I will try to explain why adult stem cells, in particular MSCs should be considered an important target for radiation-associated disease. This is also relevant in view of an increasing number of clinically approved MSC based therapies. These involve the collection of MSCs from various anatomical sites of a patient (including sites that might have been exposed to diagnostic, therapeutic or occupational ionizing radiation), followed by forced in-vitro expansion of the cells and autologous re-implantation.

We show the influence of environmental stress such as unphysiological high oxygen, radiation-induced genotoxic stress onto stemness, potency and genetic stability of MSCs.

The influence of genetic defects such as p53 mutational status or Rb1 deficiency interacts with genotoxic and cellular stress imposed on MSCs in a different manner than in cells with only limited self renewing capacity.

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