Provision and use of the ion microbeam facility SNAKE for low dose research

G. Dollinger, Universität der Bundeswehr München (UBWM)

A. Friedl, Ludwigs Maximilians Universität München (LMU)

We provide the ion microbeam irradiation facility SNAKE of the Munich tandem accelerator for precise cell and tissue irradiation giving significant access to proton and ion irradiation especially below 20 MeV/nucl for low dose research. SNAKE offers a proton microbeam with energies between 5 and 25 MeV/u giving access to low linear energy transfer (LET) particles with LET values between 2 keV/µm and 10 keV/µm. In addition, we offer deuterons, He, Li, B, C, O and even heavier ion beams at specific energies between 2 MeV/u and 8 MeV/u, thus giving access to nearly any desired high LET value between 10 keV/µm and 2000 keV/µm. Counting the ions applied to the cells or tissue gives ultimate quality of dose determination from low dose to high doses. Especially, the use of microbeam irradiations of cells and tissues allows unrivalled experiments in low dose radiobiological research, including in bystander research. An online as well as an additional offline state-of-the-art live-cell phase contrast and epifluorescence microscope allows online targeting as well as online and offline analysis of fluorescence-labelled cells for radiobiological experiments. Access to a super resolution STED fluorescence microscope is also possible. In addition, a well-equipped biolab can be used on site for radiobiological experiments at SNAKE. Established irradiation set-ups, biological materials and experimental protocols for investigating endpoints in cells and tissue like cell survival, the analysis of DNA lesions and repair, protein recruitment to damage sites, epigenetic alterations, cell-cycle effects, induction of apoptosis and chromosomal damage, are offered to be used for radiobiological research. Specific irradiation protocols as well as endpoints which extend the already used ones will be developed on request. The research will be supported both by a physics-oriented research group of the UBWM and a radiobiological research group of the LMU, both having a strong scientific background in the field.

For our research using SNAKE within low dose research program, we propose to investigate in detail the fine structure of repair factors that accumulate in the surrounding of DNA double strand breaks. It has been shown that the fine structure is directly correlated with the function of the repair factors and it is likely that the structure and the function of the factors differ at various position in the cell nucleus. Thus, there might be differences in the DNA repair and thus the sensitivity on irradiation at various parts of the nucleus. We want to elucidate whether and how the sensitivity of cells against irradiation damage is distributed within the cell nucleus. In order to obtain reliable information we will target certain areas in the cell nucleus, for example the rim or the center of the cell nucleus, the nucleoli, or look for differences between hetero or EU-chromatin. After irradiation, the foci will be analysed by ultra-high resolution STED microscopy to investigate the kinetics of the fine structure of repair factors.

Research interests – OKK – Országos Sugárbiológiai és Sugáregészségügyi Kutató Igazgatóság (OSSKI), Budapest, Hungary

OSSKI is a member of the CONCERT.

OSSKI is engaged in the research of biological effects of radiation, covering the whole range from physical interaction with matter to the application of radiation in medical, as well as in industrial practices. The main tasks of the Department of Radiation Medicine, are to investigate the biological effects of low and high dose irradiation and to perform biological dosimetry measurements. Scientists at the Department of Radiation Medicine at NRDRR have many years of experience studying radiation effects under in vitro and in vivo conditions. We investigated cancer incidence in mice after in utero irradiation and studied the oncogenic events leading to prenatal irradiation-induced tumors. We were among the first to investigate radiation-induced transcriptional alterations by whole genome microarrays in primary human fibroblast cells after high and low-dose irradiations. We applied a qRT-PCR based protocol detecting common deletions in mitochondrial genome to assess radiation-induced individual bystander responses and genome instability in human fibroblasts. We studied the combination of radiotherapy and anticancer immunotherapy as well as radiosenstizing gene therapy in experimental tumor models. We investigated interactions between irradiation and the immune system, with a special emphasis on the immune modulating effect of irradiation. We have been continuously involved in various EU-funded projects. The effect of low dose irradiation on the immune system in general and on specific cellular compartments of the immune system was the topic of the EU-FP6-NOTE project. The role of exosomes in mediating radiation induced bystander signals was studied in the frame of the DoReMi project. Radiation induced inflammatory reactions at the level of blood-brain barrier (pericytes and endothelial cells) and mitochondrial damage in the brain was studied in the frame of EU-FP7 CEREBRAD and DoReMi projects. Recently we have started investigating radiation-related biomarkers as well as immune related markers of therapy response in cancer patients subjected to radiotherapy.

The department is equipped with all the necessary equipment for cellular, molecular biological and immunological experiments (FACS, fluorescence microscope, multifunctional plate reader, fluorescent microscope, cell separation systems, and fully equipped cell culture and histology labs). In addition it has access to an animal house and irradiation facility (both X-ray and gamma source). At present the personnel of the department consists of 15 people, out of which 4 senior scientists, 2 postdocs and 7 junior scientists, PhD and graduate students. The department is involved in routine biodosimetry activities and in various training and educational activities in the field of radiobiology, radiation protection, gene and immuno-therapy for graduate and post-graduate students, as well.

In the frame of the CONCERT call we are interested in the Health topics. Our main research interests include:

- in vivo and in vitro studies of radiation induced cellular and molecular damage in various tissues after various irradiation scenarios (local or total body irradiation or internal contamination). Specifically we have experience in investigating mitochondrial damage, DNA damage, expression profile changes, immune- and inflammation-related alterations

- identification of soluble biomarkers of radiation exposure and/or radiation-induced side effects both in experimental animals and in biological samples from patients. The study of exosome mediated radiation effects in vivo is a main focus of our research.

Belgian Nuclear Research Centre (SCK•CEN)

Research interests

Cardiovascular diseases

- The vascular endothelial cell response following exposure to (low) doses of acute or chronic low- and high-LET ionizing radiation
- Direct and late effects of ionizing radiation on mitochondrial function in human endothelial cells
- The role of intercellular communication in low dose radiation-induced atherosclerosis

Neurobiology

- Investigation of radiation-induced neural tube and eye defects after irradiation during the early embryonic stage (E7.5), and evaluation of potential radioprotective agents (folic acid)
- Estimation of early and late radiation-induced brain defects after *in utero* (E11) and postnatal (P10) radiation exposure in mice
- Analysis of the role of p53 and its target genes in the long-term effects of *in utero* (E11) brain irradiation, and evaluation of p53 inhibitors as potential protective agents
- Premature ageing and neurodegeneration after postnatal (P10) radiation exposure, using a mouse model for Alzheimer disease *(future project)*

Biodosimetry research

- Identification and functional analysis of transcriptional biomarkers (genes and exons) for exposure and sensitivity to low-dose (low-LET and high-LET) ionizing radiation

Cancer research (thyroid and breast cancer, radiopharmaceuticals)

- Genetic, epigenetic, and signal transduction pathways involved in radiation response of normal and transformed thyroid cells
- Radiation-induced molecular modulations in thyroid cells under normal conditions or in combination with iodine-deficiency, or endocrine disruptors
- Impact of radiation and iodine deficiency on the microenvironment changes in cancerous and non-cancerous breast cells
- Effects of radiopharmaceuticals on healthy peripheral tissues

Research facilities

- Irradiation facilities: X-ray (250 kV (N-250 ISO-4037) with about 7 Gy/h at 100 cm distance - 50 cm minimum distance; N-series: N-10 up to N-300 (ISO 4037) – few hundreds mGy/h at 100 cm distance; RQR series), gamma source (^{60}Co (1250 keV), ^{137}Cs (661 keV)), neutrons (^{252}Cf (~2 MeV), Am-Be (~4 MeV))
- Molecular biology: PCR, qPCR, electrophoresis, western blotting, flow cytometry, immunohistochemistry (frozen, parrafin), RNA FISH, chromatin immunoprecipitation, transfection (lipofection, nucleofection, lentiviral infection), (fluorescent) microscopy, microplate readers, Luminex multiplex protein assays, Affymetrix microarray platform
- Cell culture: class I, class II, primary cells, cell lines
- SPF animalarium

Research interests of Claudia Rübe (USAAR)

DNA damage accumulation in complex normal tissues of different mouse strains (repair-proficient and -deficient mice) during fractionated irradiation with low doses (100 mGy) and very low doses (10 mGy) (radiosensitivity of different cell types and tissues; individual radiation sensitivity)

- *Accumulation of DNA damage in complex normal tissues after protracted low-dose radiation. Schanz S, Schuler N, Lorat Y, Fan L, Kaestner L, Wennemuth G, Rübe C,* ***Rübe CE****. DNA Repair (Amst). 2012 Oct 1;11(10):823-32. (IF: 4,1)*
- *Even low doses of radiation lead to DNA damage accumulation in lung tissue according to the genetically-defined DNA repair capacity. Flockerzi E, Schanz S,* ***Rübe CE****. Radiother Oncol. 2014 May;111(2):212-8. (IF: 4,4)*
- *Inducible response required for repair of low-dose radiation damage in human fibroblasts. Grudzenski S, Raths A, Conrad S,* ***Rübe CE****, Löbrich M.Proc Natl Acad Sci U S A. 2010 Aug 10;107(32):14205-10. (IF: 9,7)*

Radiosensitivity variations dependent on age with possible differences between *in utero* irradiation, infants and older children and between young and old adults

- *DNA-damage foci to detect and characterize DNA repair alterations in children treated for pediatric malignancies. Schuler N, Palm J, Kaiser M, Betten D, Furtwängler R, Rübe C,* ***Rübe CE****. PLoS One. 2014 Mar 17;9(3):e91319 (IF: 3,7)*
- *Accumulation of DNA damage in hematopoietic stem and progenitor cells during human aging. Rübe CE, Fricke A, Widmann TA, Fürst T, Madry H, Pfreundschuh M, Rübe C. PLoS One. 2011 Mar 7;6(3):e17487. (IF: 3,7)*

DNA damage response (DNA damage recognition, repair and signalling functions**)** in tissue-specific stem cells analyzed within their physiological stem cell niche

- hair follicle stem cells in skin
  Accumulation of DNA damage-induced chromatin alterations in tissue-specific stem cells: the driving force of aging? Schuler N, ***Rübe CE****. PLoS One. 2013 May 17;8(5):e63932. (IF: 3,7)*
- spermatogonial stem cells in testis
  Persistent DNA Damage in Spermatogonial Stem Cells After Fractionated Low-Dose Irradiation of Testicular Tissue. Grewenig A, Schuler N, ***Rübe CE****. Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):1123-31.*
  Protecting the heritable genome: DNA damage response mechanisms in spermatogonial stem cells. ***Rübe CE****, Zhang S, Miebach N, Fricke A, Rübe C. DNA Repair (Amst). 2011 Feb 7;10(2):159-68. (IF: 4,1)*
- neuronal stem cells in brain
- hematopoietic stem cells
  Accumulation of DNA damage in hematopoietic stem and progenitor cells during human aging. ***Rübe CE****, Fricke A, Widmann TA, Fürst T, Madry H, Pfreundschuh M, Rübe C. PLoS One. 2011 Mar 7;6(3):e17487. (IF: 3,7)*

Fundamental molecular interactions associated with ionizing radiation and the processes leading to acute and long-term health effects (cancer and non-cancer diseases, premature ageing)

- *Ultrastructural insights into the biological significance of persisting DNA Damage foci after low doses of ionizing radiation. Lorat Y, Schanz S,* ***Rübe CE****. Clin Cancer Res 2015, submitted*
- *Accumulation of DNA damage-induced chromatin alterations in tissue-specific stem cells: the driving force of aging? Schuler N,* ***Rübe CE****. PLoS One. 2013 May 17;8(5):e63932. (IF: 3,7)*

Differing carcinogenicity dependent on radiation quality: ultrastructural characterization of DNA lesions induced by low-LET and high-LET radiation by transmission electron microscopy; research on biological micro- and nanodosimetry

- *Nanoscale analysis of clustered DNA damage after high-LET irradiation by quantitative electron microscopy - The heavy burden to repair. Lorat Y, Brunner CU, Schanz S, Jakob B, Taucher-Scholz G,* ***Rübe CE****. DNA Repair (Amst). 2015 Jan 28. pii: S1568-7864(15)00019-1.*
- *Beyond repair foci: DNA double-strand break repair in euchromatic and heterochromatic compartments analyzed by transmission electron microscopy. Lorat Y, Schanz S, Schuler N, Wennemuth G, Rübe C,* ***Rübe CE****. PLoS One. 2012;7(5):e38165. (IF: 3,7)*
- *DNA repair in the context of chromatin: new molecular insights by the nanoscale detection of DNA repair complexes using transmission electron microscopy.* ***Rübe CE****, Lorat Y, Schuler N, Schanz S, Wennemuth G, Rübe C. DNA Repair (Amst). 2011 Apr 3;10(4):427-37. (IF: 4,1)*

Infrastructures

- Low-LET irradiation at the linear accelerator (6 – 10 MV photons, dose-rate 2Gy/min)
- Immunofluorescence analysis of DNA damage foci in normal tissues
- Analysis of the DNA damage response in tissue-specific stem cells within their stem cell niche
- Ultrastructural characterization of DNA lesions by transmission electron microscopy
- Flow cytometric analysis of DNA repair factors and histone modifications
- Immunhistological analysis of radiation-induced alterations in normal tissues (proliferation, apoptosis, senescence, inflammation, fibrosis, cytokine expression)
- Computer tomography and magnetic resonance imaging in small animals

January 21, 2016
INFODAY CONCERT TOPIC 1

FRENCH HAEMANGIOMA COHORT and Biobank

Monika Frenzel, Laure Piqueret-Stephan, Michelle Ricoul, Florent de Vathaire and Laure Sabatier

In France, children presenting with a skin haemangioma during early childhood were treated with radiotherapy from 1940-1973. Epidemiological analyses of this cohort have demonstrated a 3-fold higher risk of developing cancer (especially skin, breast and thyroid cancer). The French haemangioma cohort (FHC) is exceptional as it fulfils all necessary characteristics for low dose studies (<100mGy). It allows joint epidemiological and biological analyses to be performed for direct radiation risk assessment and the study of radiation-induced pathologies, due to accurate dosimetry calculations (i.e. the dose received at all major organs, taking into account the size of the baby/child during treatment) thanks to access to radiotherapy medical records. The FHC is very homogeneous, representing a normal healthy population characterised only by a haemangioma. It contains not only patients who received radiotherapy from different sources (^{226}Ra, X-rays, ^{32}P, ^{90}Y or ^{90}Sr) but also untreated individuals or those who received cryotherapy and serve as internal controls. A long-term post-irradiation follow-up exists.

A biobank for the FHC blood samples was set up through collaborations between INSERM (U1018, Florent de Vathaire) and the CEA (Radiation and Oncology Laboratory, Laure Sabatier) during the EU project, EpiRadBio. Only donors who received radiotherapy before the age of 3 years were selected, together with respective non-exposed controls. This biobank contains cytogenetic slides of metaphase spreads for T- and B-lymphocytes as well as isolated nucleated blood cells frozen in liquid nitrogen under conditions (10% DMSO in serum) to allow future cell culture experiments and DNA and FACS analyses to be undertaken. Supplementary information on confounding factors is available for every donor thanks to a questionnaire. This includes body weight and size, type of work, smoking and consumption of alcohol, (for women) number of pregnancies, appearance of cancer/benign tumour, radiological procedures during lifetime, chronic diseases, phototype and skin type. Additionally, the blood lead concentration at the time of blood donation has been determined. All this information is essential to distinguish the effect of radiation treatment from that of other factors which might influence cancer development.

The FHC allows in vivo studies and the identification of biomarkers to develop efficient models for long-term risk estimation for pathologies induced by low doses of ionising radiation, even a long time after exposure.

We propose two major research areas using this biobank for the first **CONCERT Call TOPIC 1.**

1. **Cancer effect**
   We want to focus on the polymorphism of individual telomere length as driving force to unmask recessive radiation induced mutations and its contribution in tumoral initiation and progression
2. **Non cancer effect**
   We are interested in studying mean telomere length as biomarker and predictor/prognostic factor for cardiovascular diseases and we are also interested in performing the categorization of the FHC donors according to the DNA repair capacities and to correlate it with the appearance of cerebreal/vascular diseases and cognitive impairments studies as defined in CEREBRAD

Commissariat à l'énergie atomique et aux énergies alternatives
Centre de Fontenay-aux-Roses | 92265 Fontenay-aux-Roses
T. +33 (0)1 46548344 | F.
laure.sabatier@cea.fr
Etablissement public à caractère industriel et commercial | RCS Paris B 775 685 019

Direction Recherche Fondamentale
Programme Transversal Toxicologie
PROCyTOX

Cellular Senescence and Low-Dose Ionizing Irradiation

Carl MANN

CEA/Saclay and I2BC/CNRS/University of Paris/Saclay

Web page: http://www.i2bc.paris-saclay.fr/spip.php?article977&lang=en

Cellular senescence is a stress response of mammalian cells leading to a stable proliferative arrest associated with a characteristic transcriptome including the expression of inflammatory genes. Our group is interested in studying the potentiel of low-dose ionizing irradiation in inducing the senescence of various cell types, and the role of cellular senescence in organismal aging. We are interested in mechanisms, markers, and modulators of cellular senescence. The identification of senescent cells in mouse and man is difficult because of a relative lack of specific markers. We have identified a novel histone variant that accumulates in human fibroblasts induced into senescence by persistent DNA damage, including ionizing irradiation. We are evaluating the role of this histone variant in cellular senescence, and in collaboration with Dr. Claudia Rübe , we are evaluating it's utility in identifying senescent cells in vivo. We would like to participate in a consortium interested in studying the ability of low-dose ionizing irradiation to induce cellular senescence and premature organismal aging.

Refs:

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2. Contrepois, K., Thuret, JY., Courbeyrette, R., Fenaille, F., Mann, C. Deacetylation of H4-K16Ac and heterochromatin assembly in senescence. Epigenetics Chromatin. 29, 5-15. 2012.

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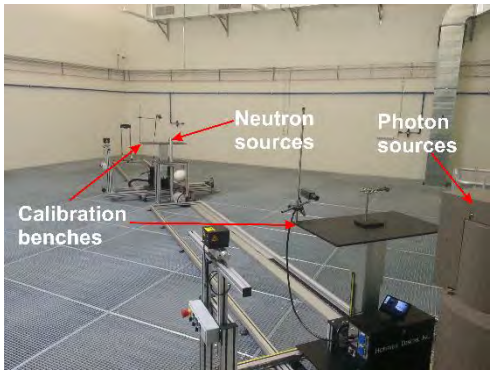
CERN Radiation Protection calibration facilities: CALLAB and CERF

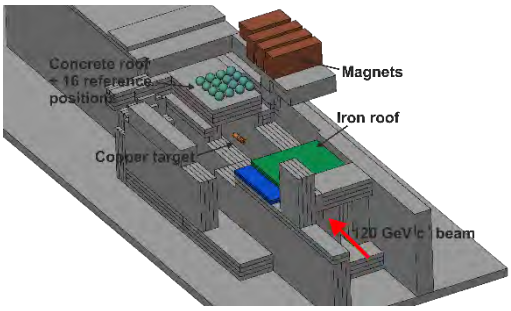
The CERN Radiation Protection (RP) group ensures that personnel on the CERN sites and the public are protected from potentially harmful effects of ionising radiation linked to CERN activities. The group assures **operational radiation protection** for accelerators, experiments and sites, which includes operational and design aspects of CERN's present and future accelerators and experiments, X-ray installations, workshops and laboratories. In addition the RP group operates: a **laboratory for alpha and gamma** spectrometry; a **high level dosimetry service** for the measurement of the radiation dose to organic materials (cable isolation, epoxy) used in accelerator components; an **individual dosimetry service** to monitor the effective doses of professionally exposed individuals; a fixed installed radiation monitoring systems comprising about 800 radiation monitors of various type; **a radioactive source service** for the purchase, loans and controls of a wide range of radioactive sources; a **radioactive waste management service** for the treatment, radiological characterization, cataloguing, conditioning and interim storage of radioactive waste. The group conducts a number of research activities and special projects, to ensure the **development** of state-of-the-art **radiation protection instrumentation** and radiation protection **calculation tools**. The group is also in charge of two RP calibration facilities: the CALibration LABoratory (CALLAB) and the CERN-EU high-energy Reference Field (CERF) facility.



CALLAB is a state-of-the-art calibration laboratory built in 2014, which provides four radiation fields:

- Photons: ^{137}Cs-137 and ^{60}Co sources (from a few µSv/h to a few Sv/h)
- Neutrons: ^{241}Am-Be ranging from $6 \cdot 10^3$ n/s (~0.1 µSv/h at 1 m) to $5 \cdot 10^7$ n/s (~700 µSv/h at 1 m)
- X-ray generator
- Beta: ^{90}Sr and ^{85}Kr sources

Simultaneous neutron and gamma irradiations are possible, providing the possibility of testing RP detectors in a mixed radiation field with varying neutron/photon ratio. The laboratory is manly used for the regular calibration of all CERN radiation protection monitors and personal dosimeters. In addition, it serves several users (both from CERN and research institutions) to test and measure the response of prototype detectors, and to study and qualify electronic components and systems. CALLAB is currently undertaking the process to obtain an official ISO/IEC 17025 accreditation for testing and calibration facilities.



The group has also been operating the **CERF facility** since more than 20 years. CERF is installed in the North Experimental Area of the Super Proton Synchrotron. A positive hadron beam (a mix of pions, protons and kaons) with a momentum of 120 GeV/c is stopped in a copper target, which can be installed under either a concrete roof-shield 80 cm thick or an iron roof-shield 40 cm thick. The neutron spectrum generated outside the concrete roof is similar to the one encountered at cruising altitudes in civil aviation and in the vicinity of high-energy accelerators. This workplace radiation field is rather unique in the world and is cited in the ISO 12789 standard. Several external users from research institutes and industrial companies worldwide come to CERF every year to test and calibrate passive dosimeters and active instrumentation. CERF is also employed for a variety of other applications such as radiobiology studies, cross section measurements, intercomparison of individual dosimeters, and calibration of in-space dosimeters.

Contacts: Pierre Carbonez: pierre.carbonez@cern.ch, Marco Silari: marco.silari@cern.ch, Fabio Pozzi: fabio.pozzi@cern.ch

Christophe Badie leads the Cancer Mechanisms and Biomarkers (CMB) group at PHE's Centre for Radiation, Chemical and Environmental Hazards. The group carries out research into the fundamental mechanisms by which ionising radiation (IR) causes cancer and conducts experimental work to identify, develop, and validate biological markers of radiation exposure, radiation-induced cancer and cancer risk assessment most specifically after low dose IR exposure (i.e. below 100 mSv).

There are two main research areas:

A. The group conducts research on haematological stem cells and the chromosomal and molecular mechanisms that underlie radiation-induced leukaemia, specifically Acute Myeloid Leukaemia (AML) initiation and development. The group investigates specific genetic factors that influence haematopoietic cell radiosensitivity and leukaemia susceptibility. There is a particular focus on the identification and characterisation of genes, which influence individual susceptibility to radiation-induced cancer. Studies of the early events in radiation leukaemogenesis are important in the context of developing mechanistic models for cancer risk estimation. Mechanistic studies on the initiation and development of radiation-induced AML are performed both with murine models and human AML samples.

B. The group is developing sensitive assays for studying IR-induced DNA damage, gene expression and epigenetic modifications to identify and validate biomarkers of exposure, individual sensitivity and cancer risk prediction. Some of these assays are being developed for biological dosimetry purposes. Other activities include the development of new technologies and the refinement of existing technologies for low dose radiation exposure assessment and effects studies (digital PCR, Molecular Counting system, Cell Sorting, New Generation Sequencing). Most group members are responsible for specific departmental duties.

Information sheet for the 27th January 2016 Information Day on the 1st Open RTD call of CONCERT

Dr **Eric BLANCHARDON** (Institut de Radioprotection et de Sûreté Nucléaire, IRSN, France)

My **Research interests** are the dosimetry of incorporated radionuclides (internal dosimetry), the biokinetic and dosimetric models, the interpretation of bioassay data, the evaluation of uncertainty and their application to dose reconstruction in epidemiological studies.

The **internal dosimetry laboratory of IRSN** can provide workforce, expertise and computer tools for the evaluation of dose resulting from intakes of radionuclides. The laboratory was involved in the former European projects Alpha-Risk (EC FP6) and Concerted Uranium Research in Europe (CURE, within DoReMi). It participates to the work of EURADOS WG7 on internal dosimetry and ICRP TG95 on internal dose coefficients. IRSN also includes laboratories dedicated to external dosimetry, biological dosimetry, epidemiology, radiobiology and radiotoxicology.

Information sheet for the 27th January 2016 Information Day on the 1st Open RTD call of CONCERT

Dr Karine TACK (Institut de Radioprotection et de Sûreté Nucléaire, IRSN, France)

As the head of the radiotoxicology laboratory at IRSN working on the effects of ionizing radiation at low doses, my research interests are related to topic 1: "Improvement of health risk assessment associated with low dose/dose rate radiation". The work of my laboratory is focused on the effects of irradiations and internal contaminations, through the case of uranium exposure or through other radionuclides in the case of the post-accidental situations.

The aim of my participation is on one hand to develop, on the basis of the CURE protocol, together with dosimetrists, epidemiologists, biologists/toxicologists and biostatisticians, a large-scale collaborative project that would allow better characterizing the biological and health effects of occupational uranium exposure.
On the other hand, I would like to have the opportunity to collaborate to projects that could be proposed on the study of low dose effects on cerebral and cardio-vascular systems, fields of research of the IRSN radiotoxicology laboratory.
This laboratory has facilities for *in vivo* experimentation for chronic exposure for both ingestion and inhalation pathways that could be used. For the research on the impact of radiation/contamination on central nervous system, technical resources such as those dedicated to the study of animal behavior or the electrophysiology for example are available.

Information sheet for the 27th January 2016 Information Day on the 1st Open RTD call of CONCERT

Dr Olivier LAURENT (Institut de Radioprotection et de Sûreté Nucléaire, IRSN, France)

As a radiation epidemiologist at IRSN, my research interests are related to topic 1: "Improvement of health risk assessment associated with low dose/dose rate radiation", with a focus on the effects of internal contamination through the case of uranium exposure.

Multidisciplinary integration is key to study the health effects low dose/dose rate radiation exposure, as emphasized by the MELODI and EURADOS Strategic Research Agendas. The Concerted Uranium Research in Europe (CURE) project supported by EU FP7 DoReMi network of excellence demonstrated the feasibility of integrating dosimetry, epidemiology and biology/toxicology to improve the characterization of the effects of uranium exposure. A full protocol was developed specifically for that purpose.

The aim of my participation is to help develop, on the basis of the CURE protocol, together with dosimetrists, epidemiologists, biologists/toxicologists and biostatisticians, a large-scale collaborative project that would allow better characterizing the biological and health effects of occupational uranium exposure. This would notably allow studying the shape of the dose-response for cancer and non-cancer outcomes, improving the knowledge of the effects of internal contamination and the understanding of radiation-induced biological mechanisms.

The CURE consortium already identified infrastructures which can be used for that purpose in Europe: epidemiological cohorts, human and animal biobanks, facilities for internal contamination, expertise in dosimetry, epidemiology, biology/toxicology and biostatistics. Contacts have already been established with potential partners beyond the initial CURE consortium, with strong potential for collaboration. Clear synergies with MELODI and EURADOS SRAs have been identified.

The laboratory of epidemiology at IRSN was coordinator of former European projects Alpha-Risk (FP6) and Concerted Uranium Research in Europe (CURE, within FP7 DoReMi). IRSN also includes laboratories dedicated to internal and external dosimetry, biological dosimetry, radiobiology and radiotoxicology.

Dr. Markus Eidemüller

Topic: Radiation risk and modelling

Helmholtz Zentrum München
Institute of Radiation Protection
85764 Neuherberg
Germany

Aims of Research

Research in the Research Group Radiation Risk is directed towards the evaluation of both the nature and level of health risks arising from exposures to all sources of ionizing radiation. A special focus is on the study of health risks associated with radiation exposures at low doses (below or of the order of 100 mSv). Such doses correspond to dose limits for occupational exposure and may be applied due to intensive medical diagnostics, e.g. by a number of CT examinations. However, the health risks of low doses are difficult to assess by epidemiological studies alone.

The aim of our Research Group is to improve qualitatively as well as quantitatively our understanding of the relationship between radiation exposures on the one hand and radiation damage to biological material and health effects to humans on the other hand. Radiation damage mechanisms are studied on a cellular level as an initiator to health effects; they include conventional direct effects to cells and tissues as well as non-targeted effects due to signalling processes. Radiobiological results are integrated in models of cancer and circulatory diseases to test whether they are expressed in epidemiological data. It is the aim to identify appropriate models for an assessment of health risks under irradiation conditions for which epidemiological data do not have sufficient power or do not exist, e.g. for low-dose or heavy-ion exposures.

Fields of research:

- Cancer risk after radiation exposure
- Biochemical-physical models of radiation effects
- Risk of circulatory diseases after radiation exposure

CONCERT Partnering Event – IARC description

IARC is a World Health Organisation (WHO) Agency. The objective of the IARC is to promote international collaboration in cancer research. The Agency is inter-disciplinary, bringing together skills in epidemiology, laboratory sciences and biostatistics to identify the causes of cancer so that preventive measures may be adopted and the burden of disease and associated suffering reduced. A significant feature of the IARC is its expertise in coordinating research across countries and organizations; its independent role as an international organization facilitates this activity.

One of the products of IARC's coordinating role is an increasingly important biobank with currently more than 10 million well-characterized samples for 1 million subjects from around the world. This resource permits the application of innovative laboratory-based methodologies to study the causes, early detection and prevention of cancer through collaborative studies with many international partners.

A core part of the Agency's mission is education and training of cancer researchers worldwide. This is achieved through fellowships, courses and publications. Priority is given to training researchers from low and middle-income countries in the areas of cancer epidemiology and cancer registration.

Training opportunities at IARC for scientists who wish to pursue a career in cancer research range from biostatistics and epidemiology to laboratory sciences, aimed at creating and facilitating collaborative research links between IARC and cancer researchers worldwide

IARC has experience in the management of large international collaborative projects in relation to cancer risk in occupational and environmental settings. The Section of Environment and Radiation (ENV) has been planning, conducting and analysing large international collaborative epidemiological studies of cancer risk associated with ionising radiation, particularly low dose protracted exposures. Its main activities include studies of the consequences of the Chernobyl accident, the International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry, European cohort study of children exposed to computed tomography scans and it has been the coordinator of numerous projects supported by the EU Euratom programme, including: case-control studies of leukaemia and thyroid cancer risk among Chernobyl liquidators from Baltic countries, Belarus and Russia, case-control studies of thyroid cancer risk in young people after the Chernobyl accident in contaminated regions of Belarus and Russia, GENE-RAD-RISK, CHILD-MED-RAD, ARCH, EPI-CT, SEMI-NUC. IARC is currently leading the coordination action “Cooperation on Chernobyl Health Research -CO-CHER” which is aiming at building partnerships with the three countries mainly affected by the accident (Belarus, Russian Federation and Ukraine), as well as with research bodies from other European countries, Japan and USA with interest in Chernobyl research in order to take the health research agenda forward.

Contact Person: Ana Belchior, anabelchior@tecnico.ulisboa.pt
Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico,
Universidade de Lisboa, E.N. 10 ao km 139,7, 2695-066 Bobadela LRS, Portugal

Research interests

Our group has been actively involved in:

- Radiobiology studies; mainly using cytogenetic assays such as, Chromosomal aberrations, Micronuclei and ɣ-H2AX assays, and Molecular biology studies.
- Dosimetry studies using Monte Carlo codes, such as MCNPX, PENELOPE and GEANT.
- Design and biological evaluation of novel target-specific radioactive compounds for nuclear imaging (PET or SPECT) and targeted systemic radiotherapy.
- Development of new chelators with different nature and charge, as well as different spacers used in bioconjugation, in order to improve targeting-properties and pharmacokinetic profiles of conjugated biomolecules.

Infrastructures

i) Laboratory for characterization of radioactive compounds equipped with radiochromatograph and radio-HPLC
ii) Laboratories for cell culture and in vitro studies (internalization, externalization, binding, cytotoxicity and radiocytotoxicity)
iii) Facilities for animal housing (normal and nude mice)
iv) Laboratory for biodistribution studies of radioactive compounds;
v) Laboratory for biochemical and molecular biology studies.
vi) Laboratories and infrastructures of support to dosimetry and metrology activities, including individual monitoring and a WBC
vii) Cobalt and Cesium irradiators
viii) Research reactor with thermal, epithermal and fast neutron beam lines

Description of the C²TN (Centro de Ciências e Tecnologias Nucleares)

C²TN is a research unit of Instituto Superior Técnico (IST), which gathers together with Technological Development Laboratories (LDTs), the main human resources, skills and research infrastructure of the former Instituto Tecnológico e Nuclear (ITN). C²TN is located on the premises of Campus Tecnológico e Nuclear (CTN), IST Pole of Loures.
This Research Center in Nuclear Sciences and Technologies is a crosscutting structure with proven expertise in Nuclear Physics & Engineering, Radiological Protection and Nuclear Safety, Radiopharmaceutical Sciences, Chemistry & Radiochemistry of *d*- and *f*-Elements, Materials Science, Nuclear and Related Techniques for characterization of Materials, Environment & Cultural Heritage. The Unit has access to specialized equipment and infrastructures, unique in the country, such as:

- Nuclear Research Reactor;
- Tandem, Van de Graaff and Linear accelerators;
- Gamma Radiation Unit; Laboratories for Synthesis & Characterization of Materials, including Low Temperatures and High Magnetic Fields;
- Facilities for Synthesis, Characterization & Preclinical Evaluation of Radioactive Tools for Nuclear Molecular Imaging and Therapy; Clean Rooms for Technological Assays.

C²TN is organized in six multidisciplinary groups contributing with their specific expertise for the Thematic Strands of the Center.

Federal Office for Radiation Protection

AG-SG1.2 Biological Radiation Effects – Biological Dosimetry

(Sabine Hornhardt, Maria Gomolka, Ulrike Kulka, Ursula Oestreicher)

Research interest:

- Molecular Epidemiology and Biobanking of radiation exposed cohorts/individuals (Kreuzer et al. 2015, Pernot et al. 2012, Weber et al. 2010)
- Radiation quality (Gomolka et al. 2005, Rössler et al. 2006)
- Radiation sensitivity (Genetic and age dependent) (Rosenberger et al. 2012, Hornhardt 2014, Kunze et al. 2015, Greve et al. 2012, Gürtler et al. 2011, Gürtler et al. 2013, Gürtler et al. 2014)
- Low dose effects (Hauptmann et al. 2016 accepted)
- Biological Dosimetry (Kulka et al. 2015, Rothkamm et al. 2013)
- Radiation induced leukemia
- Childhood leukemia (Ziegelberger et al. 2011, Fischer et al. 2015)
- Combined effects (Hornhardt et al. 2006)
- DNA repair (Rosenberger et al. 2011)

Methodology:

- Cell culture, cell survival assays, clonogenic assay, apoptotic assays, EBV immortalization of B-cells
- DNA damage response: DNA repair foci-Analyses, Comet-Analysis,
- Cytogenetic assays (FISH, mFISH, Dicentrics, micronuclei)
- Proteomics (2-D-DIGE Analysis), Western Blot, ELISA

Current Projects:

EC funding: DoReMi/CURE/Education and Training Course, EPI-CT, RENEB

National funding: ZISS, RF, INSTRA

MELODI

WHO Collaborating Center (Biological Dosimetry)

A. Wieser, C. Woda

Helmholtz Zentrum München, Institute of Radiation Protection, WG Anthropogenic Environmental Radiation, Laboratory for Retrospective Dosimetry

Helmholtz Zentrum München (HMGU) is a research institution of the Federal Republic of Germany and the Free State of Bavaria. It is divided into 33 research institutes and independent research units, which are interlinked and cooperate on various topics and in various research programs. The center has diverse technology platforms which function as central service units. To ensure rapid and efficient transfer of findings from basic research into medical applications, scientists of HMGU work closely in translational centres and clinical cooperation groups together with medical participants in the universities and hospitals in Munich.

The WG Anthropogenic Environmental Radiation of the HMGU Institute of Radiation Protection is developing methods for the assessment of radiation exposures from potential releases of radionuclides from radioactive waste disposals or by accidents in nuclear power plants, or due to terroristic acts. In the Laboratory for Retrospective Dosimetry exposure of man to radiation in the past can be detected retrospectively by measuring the absorbed dose by means of physical methods in materials of the environment, in biological tissues or in personal objects carried close to the human body. Radiation exposure which has occurred in the past was assessed retrospectively by means of Electron Paramagnetic Resonance (EPR) measurements of teeth and by thermally and optically stimulated luminescence (TL/OSL) of fired mineral containing materials such as bricks. New methods of retrospective dosimetry for radiological emergencies are developed based on analyses of the luminescence of chip cards and components of electronic devices such as cell phones and EPR measurements of touch screen glass. Recent activities include the validation of the external exposure of the Mayak Workers and Techa River Population using EPR with teeth and luminescence measurements of bricks, and investigations on the use of chip cards and portable electronic devices as emergency dosimeters.

CONCERT - Information sheet

Topic 1: Improvement of health risk assessment associated with low dose/dose rate radiation

Research focus: Low-fidelity DNA double strand break repair in leukemia-cells-of-origin

Research partners and interests

Dr. Daniela Kraft & Dr. Claudia Fournier, Biophysics Department, **GSI Helmholtz center for heavy ion research (Darmstadt, Germany)**

- **Radiation response of hematopoietic stem and progenitor cells (HSPC)**
- Isolation and culture of HSPC, differentiation in a Colony-Forming-Unit assay (CFU-assay)
- low and high LET radiation exposure
  a) X rays
  b) alpha particles, ^{241}Am-source, max. energy: 5.49 MeV, mean LET 153±45 keV/µm
  c) Radon exposure of cell cultures or small animals, simulate conditions like in radon-galleries, max. radon concentration 620 kBq/m^3
  d) heavy ion accelerators: https://www.gsi.de/en/gsiwork/accelerator.htm)
- Cytogenetic aberrations, interphase and multicolour fluorescence in situ hybridization (FISH)
- measurement of apoptosis and cell cycle parameters (FACS Canto II)

Prof. Dr. rer .nat. Lisa Wiesmüller, Department of Obstetrics and Gynaecology of the **University of Ulm (Ulm, Germany).**

- **cancer risk assessment, prediction of therapeutic responsiveness, chemoprevention, DNA repair/recombination, genotoxicity**
- Functional analysis of human peripheral blood lymphocytes, lymphoblastoid cell lines, subpopulations of human hematopoietic stem and progenitor cells
- fluorescence based system for pathway-specific DNA double-strand break (DSB) repair analysis (European patent EP1399576)
- Quantitative immunofluorescence microscopy
- screen-based identification of molecular targets in the DNA damage response
- *Mixed Lineage Leukemia* (*MLL*) gene-based reporter assay for screening compounds mitigating radiation-induced *MLL* rearrangements

Literature

Keimling M, Deniz M, Varga D, Stahl A, Schrezenmeier H, Kreienberg R, Hoffmann I, König J, Wiesmüller L. The power of DNA double-strand break (DSB) repair testing to predict breast cancer susceptibility. 2012. FASEB J. May;26(5):2094-104

Ireno, I.C., C. Baumann, R. Stöber, J. G. Hengstler L. Wiesmüller. Fluorescence-Based Recombination Assay for Sensitive and Specific Detection of Genotoxic Carcinogens in Human Cells. 2014. *Archives of Toxicology* 88 (5): 1141–59.

Gole B, Baumann C, Mian E, Ireno CI, Wiesmüller L. Endonuclease G initiates DNA rearrangements at the MLL breakpoint cluster upon replication stress. Oncogene. 2015 Jun;34(26):3391-401

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Rall, M., D. Kraft, M. Volcic, A. Cucu, E. Nasonova, G. Taucher-Scholz, H.Bönig, L. Wiesmüller C. Fournier. 2015. “Impact of Charged Particle Exposure on Homologous DNA Double-Strand Break Repair in Human Blood-Derived Cells.” *Frontiers in Oncology* 5: 250.

Pavel Kundrát, PhD
Research Group Radiation Risk
Institute of Radiation Protection
Helmholtz Zentrum München – German Research Center for Environmental Health
pavel.kundrat@helmholtz-muenchen.de, Phone: +49 89 3187 4114

Expertise: Multi-Scale Modelling of Biological Effects of Radiations

- Track structure-based modelling of DNA damage induced by radiation of diverse quality [1-2]
- Cellular repair/misrepair of radiation-induced damage [3-4], induction of chromosome aberrations [5]
- Models of cell killing/survival [6-7]
- Mechanistic modelling of bystander effects [8]
- Multi-scale modelling of intercellular communication [9-10]

[1] Friedland W, Dingfelder M, Kundrát P, Jacob P. 2011 Track structures, DNA targets and radiation effects in the biophysical Monte Carlo simulation code PARTRAC. Mutat Res 711:28-40.

[2] Schmitt E, Friedland W, Kundrát P, Dingfelder M, Ottolenghi A. 2015 Cross-section scaling for track structure simulations of low-energy ions in liquid water. Radiat Prot Dosimetry 166:15-8.

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[4] Friedland W, Kundrát P, Jacob P. 2012 Stochastic modelling of DSB repair after photon and ion irradiation. Int J Radiat Biol 88:129-36.

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[6] Kundrát P. 2006 Detailed analysis of the cell-inactivation mechanism by accelerated protons and light ions. Phys Med Biol 51:1185-99.

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Ladislav Tomasek

Project proposal will be related to Topic 1

Contribution of SURO in Concerted Uranium Research in Europe (CURE) Project

The National Radiation Protection Institute (SURO) intend to participate in the Concerted Uranium Research in Europe (CURE). The contribution of SURO will include epidemiology, dosimetry, biology (pilot molecular epidemiology), and uncertainty tasks. The protocols were developed from existing European cohorts of workers exposed to uranium (miners and nuclear industry employees involved in the nuclear fuel cycle) together with expertise in epidemiology, biology and dosimetry of CURE partner institutions. SURO will be participating together with German and French partners in studies of uranium miners. The importance of the Czech study of 10 000 underground miners is in relatively high exposures and their estimates which depend on detailed monitoring in the mines. In coordination with other partners, the study will be related to low doses. The effects for different endpoint (lung cancer, leukaemia, or other cancers) will be evaluated in relation to relevant doses which include internal doses from inhalation of radon and long lived radionuclides in the dust. The estimation of the latter doses depend on several parameters like particle size, solubility, and isotopic composition. These parameters were recently analysed in Czech uranium mines (Rozna) which are still operated. Additional analyses could be conducted within chemical processing milling plant. This will also contribute to individual evaluation of biomarkers collected from biological samples of active miners and millers.

Radiobiology and Biophysiscs Group, Department of Life and Environmental Physics, DFVM
"Horia Hulubei" National Institute for Physics and Nuclear Engineering, IFIN-HH
Bucharest-Magurele, Romania

Research interest:

1. Our main research interest resides in the area of genetic, epigenetic, non-targeted effects (adaptive and bystander response) induced by physical (low dose and low dose rate irradiation) and chemical agents (chemotherapeutic agents, radiomimetics). We are specifically interested in deciphering how compartmental/organellar signalling mechanisms contribute to these effects. Thus we address the role of ER stress, mitochondrial stress and cytoplasmic stress in transmission of bystander effects as well as their contribution to participate in adaptive responses that are consequent to DNA damage induced by irradiation and radiomimetics. For this approach we use in vitro cell models comprising human and rodent cell lines, particularly fibroblasts and brain cells. We are expanding this area of research to identify particularities of these signaling mechanisms in immune cells (from brain and circulating blood) to evaluate the contribution of the immune system in transmitting bystander effects and inducing adaptive responses.

2. A significant research interest of our group is to study the individual susceptibilities to low doses of radiation. For this we will use samples from patients undergoing both diagnostic and therapeutic irradiation. We propose to identify the sensitive persons and to potentially identify the biomarkers of exposure.

Methods: cytogenetics: micronuclei, G2 assay; microscopy techniques: immunofluorescence, monitoring calcium flux, mitochondrial transmembranar potential; fluorescence spectroscopy (steady-state, lifetime); spectroscopy (UV-VIS, IR, AAS); molecular approaches: DNA damage and repair (comet assay, γ-H2AX foci and 53BP1 foci), markers of oxidative stress (antioxidant activity, lipid peroxides level, protein carbonylation, ROS level), ELISA, viability assays, apoptosis, clonogenic survival, gene expression (RT-PCR), protein expression (Western blotting).

Infrastructure: complete cell cultures laboratory (laminar flow cabinets, CO2 incubators, inverted microscopes with CCD camera, stereomicroscope, thermostated baths, sterilizer, refrigerated centrifuges, dedicated rooms with controlled climate – clean rooms, liquid Nitrogen tanks etc.); PCR machines (real time PCR), DNA electrophoresis and UV transiluminator; spectrophotometer UV-VIS Cary 100 (Varian), spectrofluorimeter FluoroMax 3 (Horiba Jobin Yvon), time resolved fluorimeter (based on PicoQuant components), a Horiba Fluorolog modular spectrofluorometer with monochromator and two photomultiplier units, FTIR spectrometer Tensor 27 (Bruker), multiplate reader Mithras (Berthold), comet assay system (including acquisition system Comet Assay IV, Perceptive instruments), up-write fluorescence microscope BX 51 (Olympus), inverted fluorescence microscope IX71 (Olympus) equipped with Polychrome V illuminator (Till Photonics) and Ar laser (Melles Griot) as excitation sources, iXon EM camera (Andor), motorized stage (Prior), filter wheel (Sutter) in the emission path and thermostated Petri dishes holder, all setup is controlled by iQ software (Andor), Avanti JXN-30 Centrifuge, various shakers, flow cytometer CellLab Quanta (Beckman Coulter), **standard chemistry laboratory infrastructure** (ultrapure water devices, fume cupboards, incubators, peristaltic pumps, balances, pH-meter, liposome extruder, ultrasonic bath, etc.), **animal house for small animals** (mice, rats, Guinea pigs, rabbits); f**acilities for ultra low level laboratory**; **external irradiation facilities** (XSTRAHL XRC 160 X-rays machine, UV lamp (UV-C and UV-B) with posibility to flux measurement); radiation counters (gamma, beta).

Access to genetic laboratory: Sanger Sequencing: ABI 310, CEQ 8000, PyroMark 24; Next Generation Sequencing: Ilumina MySeq; Microarray: Agilent DNA Microarray Scanner G2565CA, Real Time PCR:ABI 7000, Roche 480, RotorGene 6000.
Access to the X-rays machine from hospital: Primus Siemens (6MV)

The Laboratory of Radiation Biology and Biomedicine of the ENEA has a strong experience in low-dose risk research applied to cancer effects. A main focus of its activities for several years has been in animal radiation research for investigation of the mechanisms of radiation oncogenesis and tissue response to low/intermediate dose ionizing radiation.

The laboratory has also acquired significant expertise regarding non-cancer effects of radiation, including cardiovascular and cerebrovascular disease and lens opacity, with emphasis on the mechanistic aspects and molecular pathogenesis of radiation-induced disease after low dose exposure.

The laboratory has participated in several EURATOM projects, the most recent of which are the FP7 projects DoReMi, RENEB, ProCardio, CEREBRAD, Dark-Risk and OPERRA. ENEA is committed to encouraging excellence in radiation protection research and has joined the European platforms MELODI and EURADOS.

In detail, main research interests are:

Cancer effects

- To provide quantitative data on radiation oncogenesis at low doses using well established mouse models of cancer.
- To identify the target cells for radiation oncogenesis that may have specific responses to radiation
- To investigate the contribution of epigenetic modifications to cancer risk from exposure to low/moderate dose of radiation.
- To identify and validate biomarkers of exposure and health effects related to cancer**.**

Non-cancer effects

- To provide *in vitro/in vivo* models of radiation-related non-cancer diseases, including specific models of cardiovascular/cerebrovascular and cognitive diseases, lens opacities, and other tissue injuries will help clarify the regulatory pathways involved.
- To determine the shape of dose-response relationship for cardiovascular/cerebrovascular and cognitive diseases, lens opacities, and other non-cancer tissue injury at low or moderate doses.
- To identify, develop and validate early and late biomarkers of exposure for non-cancer diseases.

François Boussin, Head of **Laboratoire de RadioPathologie iRCM-UMR 967, CEA**, Fontenay-aux-Roses, France
Email: boussin@cea.fr
Tel 33 1 46 54 97 91
Key Words: **neural stem cells/DNA damage response/mouse models/neurogenesis, radio-induced behavioural and cognitive impairments.**

Our aims are 1) to analyse the molecular and cellular effects of ionizing radiation on the developing and adult brain at short and long terms and 2) to determine their cognitive and behavioural consequences. Our research is particularly focused on the effects of low-dose radiation on neural stem cells and neurogenesis. We are interested in deciphering the DNA damage response of neurogenic cells and the radio-induced changes of their microenvironment. To this aim we compare WT mice with mouse models moderately deficient for DNA repair.
We are involved in the RISK-IR (Euratom) project.

Publications 2012-2015

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2. Cell Sorting of Neural Stem and Progenitor Cells from the Adult Mouse Subventricular Zone and Live-imaging of their Cell Cycle Dynamics. **Daynac M, Morizur L, Kortulewski T, Gauthier LR,** Ruat M**, Mouthon MA*, Boussin FD**.***J Vis Exp.** 2015 Sep 14;(103).
3. Brain development is impaired in c-fos -/- mice.Velazquez FN, Prucca CG, **Etienne O,** D'Astolfo DS, **Silvestre DC**, **Boussin FD***, Caputto BL.***Oncotarget**. 2015 Jul 10;6(19):16883-901.
4. Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors.
5. Flynn RL, Cox KE, **Jeitany M**, Wakimoto H, Bryll AR, Ganem NJ, Bersani F**, Pineda JR**, Suvà ML, Benes CH, Haber DA, **Boussin FD**, Zou L. **Science**. 2015 Jan 16;347(6219):273-7.
6. TGF β lengthens the G1 phase of stem cells in aged mouse brain. **Daynac M, Pineda JR, Chicheportiche A, Gauthier LR, Morizur L, Boussin FD*, Mouthon MA*. Stem Cells**. 2014 Dec;32(12):3257-65.
7. Assessing cell cycle progression of neural stem and progenitor cells in the mouse developing brain after genotoxic stress. **Etienne O, Bery A, Roque T, Desmaze C, Boussin FD**. **J Vis Exp**. 2014 May 7;(87). doi: 10.3791/51209.
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13. Partial complementation of a DNA ligase I deficiency by DNA ligase III and its impact on cell survival and telomere stability in mammalian cells. Le Chalony C, **Hoffschir F, Gauthier LR,** Gross J, Biard DS, **Boussin FD*,** Pennaneach V*. **Cell Mol Life Sci**. 2012 Sep;69(17):2933-49.
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Werner Friedland, PhD
Research Group Radiation Risk
Institute of Radiation Protection
Helmholtz Zentrum München – German Research Center for Environmental Health
friedland@helmholtz-muenchen.de, +49 89 3187 2767

Core Expertise: Track Structure-Based Modelling of Biological Effects of Radiations of Diverse Quality

For more than 20 years the multi-scale biophysical research Monte Carlo code PARTRAC [1] has been developed and applied to studies of DNA damage induction and repair on cellular level. PARTRAC comprises

- track structure calculations for photons (0.1 keV-1.3 MeV) in any material, electrons (10 eV – 10 MeV) and ions [2] (1 keV/u – 1 GeV/u) in liquid water;
  special applications: electrons in gold (100 eV – 1 MeV) [3], ^{125}I and ^{131}I decay [4]
- radiation chemistry model in liquid water ($^{\bullet}OH$, H_3O^+, H_2O_2, OH^-, H_2, $H^{\bullet}$,e_{aq}) [5]
- multi-scale model of DNA in human fibroblasts and lymphocytes including nucleotides and nucleosomes in atomic resolution, chromatin fiber structure and loops, chromosome domains and chromosomes, hetero- and euchromatin structures
- DNA damage induction, simulated by superposition of tracks, chemistry and DNA models; direct and indirect effects included; distinguishing single- and double-strand breaks, local and regional DNA damage clusters, base lesions, dose-dependent DNA fragmentation
- DNA damage response model, describing NHEJ repair pathway; starting from the calculated initial DNA damage, tracking spatial mobility and enzymatic processing of the broken DNA ends until final (correct or incorrect) rejoining [6]
- Chromosomal aberration model, extending the NHEJ repair model by explicitly considering centromeres and scoring the rejoining between DNA ends from different chromosomes [7]

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[7] Friedland et al 2013 Mutat Res 756:213-223

- **Who we are**

Umberto Galderisi
Department of Experimental Biology – Second University of Naples – Italy

- **What are our research interests**

The major target of low dose effects may be stem cells. As result of their long life, stem cells may undergo several rounds of low-level radiation damage that, taken singly, may not have a big impact on cellular physiology, but collectively, these rounds of radiation may severely affect cellular function. We study the effect of low dose radiation on mesenchymal stem cells (MSCs). These cells are of great interest since, besides their ability to differentiate in bone, cartilage and fat; they support hematopoiesis; contribute to the tissue repair; and modulate inflammatory response. The activities of MSCs are accomplished mainly by the secretion of cytokines and growth factors. Low dose radiation induces senescence of MSCs, which profoundly affects the composition of MSC secretome.

Factors secreted by senescent cells could constitute a danger signal that sensitizes normal neighboring cells to senesce. This may reduce the possibility of damaged cells at risk of neoplastic transformation failing to enter senescence. There are also potential negative consequences of the presence of senescent cells in a tissue. A few senescent cells may sensitize many neighboring healthy cells to senesce with the accumulation of a huge number of senescent cells that in impair tissue function and contribute to organismal aging.

I. Currently, we are studying changes in composition of MSC secretome following low dose exposure.
II. We have identified in vitro some key factors (Insulin growth factor binding proteins) that are upregulated in the secretome of low dose irradiated MSCs. These proteins are responsible of senescence induction in healthy cells.
III. We have a pilot study on patients undergoing low dose exposure (CT scan) to evaluate levels of Insulin growth factor binding proteins. Preliminary data showed that there is a significant increase following CT scan analysis.
IV. We are interested in comparison studies on the effect on MSCs of low dose radiation from different sources (gamma rays; X rays; alpha particles) to evaluate safety and biological outcomes.
V. We are interested in secretome analysis of other stem cell types following radiation exposure.

- **Where are we**

The Department of Experimental Medicine includes preclinical and clinical disciplines, all perfectly integrated and culturally joined.

The Department is organized into different divisions that represent a solid base for a link among different disciplines in the conduction of research programs.

The Department includes the following Divisions: Human physiology and Integrated Biological Functions and Histology, Pharmacology, Microbiology and Clinical Microbiology, Biotechnology and Molecular Biology, Public Health, Occupational Health and Legal Medicine and it also includes a number of laboratories, equipped with modern and complex instruments. Several research projects have been financed and more than 250 scientific papers have been published in the last five years.

27th of January, 2016 - Information Day on the 1st OPEN RTD CALL of CONCERT

Sophie JACOB, PhD, sophie.jacob@irsn.fr

Epidemiologist

INSTITUT DE RADIOPROTECTION ET DE SURETE NUCLEAIRE, IRSN, France

Topic 1: Improvement of health risk assessment associated with low dose/dose rate radiation

I am a radiation epidemiologist with particular interest for radiation-induced **cardiac toxicity** in the context of **chest radiotherapy**. I focused my research on radiotherapy for breast cancer that can lead to secondary cardiac effects due to the presence of neighboring cardiac normal tissues within the irradiation field (heart absorbed doses per fraction: around 200 mSv or lower). Previous studies showed an increased long-term cardiovascular mortality/morbidity after radiotherapy for breast cancer. However, there is still a lack of knowledge for **early cardiotoxicity** that can appear long before the onset of clinically significant cardiac events.

In 2015, we launched the French BACCARAT study. Based on a 2 year follow-up prospective cohort of patients treated with breast RT (3D-CRT), it aims to enhance knowledge on the risk of early **subclinical** functional and anatomical cardiac modifications *(occurrence and progression of early subclinical cardiac lesions, detected by strain echocardiography and Coronary Computed Tomography Angiography),* combined with simultaneous assessment of multiple circulating **biomarkers** of cardiac lesions *(microvascular rarefactions, coronary damage, tissue inflammation)* and accurate heart **dosimetry** *(heart absorbed doses, not only for whole heart but also for its substructures*). Finally, we plan to propose multivariate model of normal tissue complication probability (**NTCP**), which takes into account all these clinical, biological and dosimetric parameters and will offer a powerful approach to the improvement of radiation-induced cardiovascular disease risk assessment.

This national study is based on a multidisciplinary approach and collaboration combining radiation, cardiologic and molecular epidemiology, biostatistics, clinical research, oncology, radiotherapy, dosimetry and radiobiology. This is a **pilot epidemiological study** that we propose to integrate in a large European collaboration on the study of radiation-induced cardiac toxicity in the context of chest radiotherapy.

In the field of health risk assessment associated with low dose/dose rate radiation, I have a previous experience with the French O'CLOC study on the risk of cataract among interventional cardiologists that was integrated in DoReMi Network of Excellence and contributed to provide materials and methods for the launch of a large European cohort (EURALOC project – OPERRA call 2013) which is a multidisciplinary project combining ophthalmologists, dosimetrists and clinicians ophthalmologists.

In the frame of projects on radiation-induced cardiac toxicity in the context of chest radiotherapy, IRSN has laboratories dedicated to epidemiology, external dosimetry and radiobiology.

Radiation Immunobiology at the Department of Radiation Oncology of the Universitätsklinikum Erlangen (UKER)

Lead scientists:

Prof. Udo Gaipl (Head of Radiation Immunobiology) and Dr. Frey (Lab-Manager and person in charge for pre-clinical animal models)

Research interests:

We focus on the role of the immune system in the response to radiation. Different aspects are addressed, in particular (1) mechanistic fundamentals for attenuation of inflammation after exposure to low doses of radiation (X-ray and radon), (2) induction of anti-tumor immunity by combination of radiation with immune modulation by vaccination, hyperthermia, and/or checkpoint-inhibitors, (3) detailed immunophenotyping of patients with cancer and non-cancer diseases before, during and after exposure to local and systemic radiation alone or in combination with additional cytotoxic agents, (4) impact of radiation on immune editing in general, since low, intermediate and high radiation doses impact on the tumour cell microenvironment and thereby on both, carcinogenesis and induction of anti-tumor immunity.

Infrastructures:

We offer a multicolor-flow-cytometry-based detailed immunomonitoring of persons exposed to radiation. For this DIoB assay (Detailed Immunophenotyping of peripheral human whole Blood samples) only 2.5ml of whole blood are needed.

Further, we set up small animal radiation procedures allowing the evaluation of the immunogenic potential of local exposure to radiation in different doses, fractionation regiments alone and in combination with further immune modulation based on mainly syngeneic mouse models.

Additionally, functional *ex vivo* assays with cells exposed to stressors such as radiation and immune cells such dendritic cells, macrophages, natural killer cells and T cells are established.

The radiation is performed with an X-ray generator Isovolt Titan (Ge Inspection Technologies), therapeutic linear accelerators that are in routinely clinical use for tumour therapy, or with orthovoltage technique (Stabilipan).

Introduction to Finnish Consortium on Radiation Safety Research (CORES)

Prof. Sisko Salomaa
University of Eastern Finland and STUK – Radiation and Nuclear Safety Authority

Based on the Government Resolution, a process was initiated in 2013 to strengthen the co-operation between STUK and universities and create a national research consortium that would carry out research on various aspects of ionizing and non-ionizing radiation safety. This process has involved an analysis of scientific disciplines required for radiation protection and surveying the profiles of Finnish universities. Existing collaborations were formalized and additional competencies were identified. The first version of a National Program for Radiation Safety Research was published in collaboration of STUK and nine universities in 2015. Research areas for the national program include health (low dose risk as well as medical use of radiation), environment (radioecology) and emergencies (emergency preparedness and response, security of sources). As cross cutting themes risk assessment, risk management as well as technological development (metrology and dosimetry) are addressed. Overall, the program is well aligned with the objectives of the European radiation protection research platforms (MELODI, ALLIANCE, NERIS, EURADOS), with additional elements relevant for non-ionizing radiation safety, security research and metrology research. The co-operation network also involves several university hospitals, with access to patient materials and high quality dosimetric information systems and great potential for register-linked studies
https://www.stuk.fi/documents/12547/719505/kansallinen_sateilyturvallisuustutkimuksen_ohjelma.pdf/27c00dbe-4e2f-4ca4-9d7b-5f29f257eef6

The Agreement on National Consortium for Radiation Safety Research between STUK and nine universities was signed in 2015. In addition of STUK, the following universities have contributed to the national program: University of Eastern Finland, University of Jyväskylä, University of Tampere, Tampere University of Technology, University of Helsinki, Aalto University, Lappeenranta University of Technology, University of Oulu and University of Turku. Based on the Government Resolution, the Agreement on National Consortium for Radiation Safety Research provides the legal link for the beneficiary-Linked Third Party-relationship between the members of the Consortium.

University of Eastern Finland, Department of Environmental and Biological Sciences

The University of Eastern Finland (UEF) is one of the largest universities in Finland. The Biological effects and health risks of radiation is among the focus areas of the Department of Environmental and Biological Sciences. We have extensive experience of research in biological effects and health risks of radiation, including both ionizing and non-ionizing radiation. All approaches of environmental health research are used, including *in vitro* studies, animal studies, epidemiology and exposure assessment. Our recent research has focused particularly on cancer-related effects (of ionizing and non-ionizing radiation) and has included measurements of DNA damage and repair, genomic instability, gene expression changes, and epigenetic effects including miRNA.

State-of-the-art facilities for cell culture, and cell and molecular biology are available as well as access to the animal facilities of the UEF. Radiobiological research is conducted in collaboration with the Cancer Centre of the Kuopio University Hospital, which offers a possibility to obtain samples from radiotherapy or diagnostic radiology patients.

Contact persons: Prof. Sisko Salomaa (present at Info Day), Prof. Jukka Juutilainen, Adjunct Prof. Jonne Naarala, Dr. Päivi Roivainen (present at Info Day).

CONCERT Information Day on the 1st OPEN RTD CALL, 27th January 2016, Munich

Participants from the University of Pavia:

- **Andrea Ottolenghi**, andrea.ottolenghi@unipv.it
- **Giorgio Baiocco**, giorgio.baiocco@unipv.it
- **Gabriele Babini**, gabriele.babini@unipv.it
- **Jacopo Morini**, jacopo.morini@unipv.it

Call topics:

Topic 1: Improvement of health risk assessment associated with low dose/dose rate radiation

Topic 2: Reducing uncertainties in human and ecosystem radiological risk assessment and management in nuclear emergencies and existing exposure situations, including NORM.

Radiobiology and Radiation Biophysics Group (lead by Andrea Ottolenghi, Physics Department, University of Pavia, Pavia, Italy)

The group carries on experimental and theoretical studies on ionizing radiation effects (particularly after low doses), with applications in the clinical use of radiation for diagnostics and therapy (including the risk of complications and secondary tumours), and radiation protection, also for manned missions in deep space. The general objectives are:

i) to understand the mechanisms and to develop mathematical models of the action of different qualities of radiation on biological systems, from physical interactions to biological effects at the sub-cellular and cellular level, which can further drive effects at the tissue, organ and systemic level (e. g. cancer and non-cancer, including cardiovascular effects). The research focuses on radiation-induced DNA damage and repair processes, intra- and extra- cellular signalling perturbation, and their anti- and pro-carcinogenesis implications. Radiation is studied as a perturbing agent of complex systems that alters the complex behaviours and feedback phenomena, and may end up with either the recovery of a homeostatic equilibrium or with pathological conditions. Classical reductionist studies are combined with system, multi-scale approaches (systems radiation biology), also to integrate datasets on different radiation effects (e.g. pro-inflammatory responses, cell senescence);

ii) to use radiation as a probe to study the response of biological systems to external stimuli, e.g. for individual sensitivity studies, also for patients with (rare) genetic diseases.

Involvement of the group in Research and Training EURATOM Programmes in the 7th Framework and in HORIZON 2020

Local (UniPv) scientific management of the EURATOM projects CONCERT (with coordination of the WP on E&T), OPERRA, EUTEMPE-RX, ANNETTE, DoReMi (with coordination of the WP on E&T), EPIRADBIO. EU coordination of the EURATOM projects ANDANTE and ALLEGRO.

Reference people for different research activities/expertise

Andrea Ottolenghi, physicist, head of the Radiobiology and Radiation Biophysics Group: research on the effects of low doses of different qualities and on risk assessment, with applications to radiation protection and medical use of radiation.

Giorgio Baiocco physicist: theoretical models and simulations of radiation transport and effects on biological structures (from the macroscopic to the cellular/sub-cellular scale, with track structure modeling).

Gabriele Babini physicist: experimental and theoretical studies on intra-/extra-cellular signaling, bioinformatic analysis of high throughput datasets and modeling of radiation action with a systems radiation biology approach.

Jacopo Morini, biologist: experimental and theoretical studies on intra-/extra-cellular signaling, individual radiosensitivity (also with applications to rare diseases) and DNA damage response to ionizing radiation.

Austrian Agency for Health and Food Safety (AGES), Austria

Division Radiation Protection

The Division Radiation Protection of the AGES – as the Technical Support Organisation of the Ministries of Environment and Health - covers a wide range of radiation protection issues.

The AGES hosts the National Radon Centre of Austria, which is in charge of coordinating the radon work and strategy in Austria. It has an excellent expertise and comprehensive equipment for radon measurements, hosts the national radon database and carries out research projects and pilot studies on specific topics in the field (e.g. radon and geology/geogenic parameters, structural radon protection, radon at work places). Dose assessment at NORM and radon workplaces is also in the responsibility of the division.

Nuclear Emergency Response and Environmental and Food Monitoring are other major work areas of the division. A laboratory-based monitoring network is run by the AGES. Various environmental media such as air, precipitation, soil and surface water and wastewater treatment plants are sampled, measured and assessed. In addition, AGES performs a comprehensive monitoring of food (e.g. milk, diet) to avoid highly contaminated food getting on the table and to determine the annual ingestion dose. Some special monitoring programmes are carried out, e.g. a radio-ecological database has been created since 1992 by systematic yearly sampling of various environmental and food samples. Aerosol attached radionuclides are continuously measured on the interdisciplinary Alpine measurement and research station “Sonnblick” at 3.100 m. In addition special radio-ecological, food and environmental projects were carried out (e.g. radionuclides in ground- and drinking water, meat, mushrooms, RN distribution in soil).

Furthermore, the Radiation Protection Division runs the Reference Center for technical Quality Assurance, which carries out quality assurance measures as part of the Breast Cancer Early Detection Programme.

For all these tasks the EN ISO 17025 accredited laboratories of the Radiation Protection Division are well-equipped with instruments for alpha- and gamma-spectrometry, LSC, ICP-MS and radon measurements. The division is well connected and cooperates with Austrian and International research institutes and universities, as well as authorities and international institutions (EC, IAEA, WHO).

The main research interest of the AGES, Division Radiation Protection, within CONCERT is in the field of radon, radioecology and nuclear emergency situations. The division has a high expertise in this field, has access to (long-term monitoring) data (radon, radionuclides in different media) for Austria, well equipped laboratories and good connections to other research institutes and authorities for possible co-operations.

Contact:
Dr. Valeria Gruber
Austrian Agency for Health and Food Safety (AGES), Division Radiation Protection
Department for Radon and Radioecology
National Radon Centre of Austria
Wieningerstrasse 8
A-4020 Linz, Austria
Tel. ++43-(0)50555-41906
valeria.gruber@ages.at
www.ages.at

Topic 1: Improvement of health risk assessment associated with low dose/dose rate radiation

Research Opportunities with low- and high-LET Microbeam Irradiations - Access to the PTB Microbeam Facility

Ulrich Giesen
Physikalisch-Technische Bundesanstalt
Bundesallee 100
D-38116 Braunschweig
Germany
Ulrich.giesen@ptb.de

The PTB accelerator facility (PIAF) for ion and neutron research [Bre80] and the charged-particle microbeam [Gre04] are established user facilities, which have been involved in a variety of international projects and European framework programmes. The microbeam facility has been in routine operation for more than 10 years and irradiations of various cell types have been carried out for a variety of collaborative projects with outside groups. In particular, the PTB-microbeam has been part of the INTERSTANDER project for the investigation of bystander effects [Fra06, Fra08, Gre06, Hel07] and the BioQuaRT project [Pal15].

The microbeam provides high-LET α-particles and low-LET protons with energies of 3 MeV to 20 MeV. This range of ions and energies allows the selection of radiation qualities with LET values between 3 and 200 keV/µm, which covers almost entirely the range from diagnostic X-rays to naturally occurring α-radiation. With the charged-particle microbeam, substructures (cell nucleus or cytoplasm) of individual cells can be targeted with a spatial resolution of about 2 µm and irradiated with a single or with precisely counted multiple particles. For the study of bystander effects one can choose to target selected cells or a fraction of cells in a dish and study the radiation response in directly irradiated and bystander cells. Presently up to 50.000 cells per hour can be automatically processed including all experimental steps (imaging, cell recognition, position analysis and irradiation). The use of reference markers allows revisiting of each cell in a dish for later analysis of radiation response using a variety of endpoints. Live-cell imaging of GFP- or RFP-tagged reporter genes has been established at PTB and is available [Gie10, Mos11].

In addition to microbeam irradiations also broadbeam irradiations with protons or α-particles and irradiations in neutron fields with energies in the range of 0.1 MeV to 15 MeV can be made available [Fra10, Hei05, Sch03].

An S1 laboratory for cell culture and microbiological preparations is available in close proximity to the microbeam facility. The local research team will carry out all the procedures at the microbeam and will support the external partners as much as possible. We can provide access to the biology laboratory well ahead of the scheduled microbeam time for initial preparations and developments, studies of backgrounds (γ-H2AX, etc) and controls, as well as tests using an α-source. There is a guest house on site and a hotel is located close to PTB.

In summary, the experimental conditions are perfectly suited for external research groups studying in detail biological effects at the level of individual cells (or co-cultures) with single particles, low doses or inhomogeneous dose distributions.