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EJP-CONCERT

European Joint Programme for the Integration of Radiation Protection Research

H2020 – 662287

D9.100 - Report on LEU-TRACK related dissemination and training activities

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Reviewer(s): Géza Sáfrány
and CONCERT coordination team

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Abstract

The main objective of the deliverable was to educate and train young scientists in practical, theoretical and presenting skills through the active participation in the project meetings and national and international conferences. The second aim was to disseminate the results of this project to radiobiological communities as well as stakeholders by means of oral and poster presentations and scientific peer-reviewed publications. For this purpose, LEU-TRACK organised three workshops, one for practical laboratory skills, one for presentation skills and one for dissemination of project results. The students involved in this project participated in numerous national and international courses and meetings to learn and to exchange knowledge with peers and experienced scientists.

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1 Education

The LEU-TRACK project was responsible for the academic education of two PhD students, two MSc students and three BSc students most of whom were at least partly financed by the project.

PhD students:

Dávid Kis, NNK, 01/2019-03/2020. His PhD was partly funded by a grant awarded by the Semmelweis University, Budapest, Hungary; Eric Andreas Rutten, PHE, 03/2018–03/2020.

MSc students:

Dávid Kis, NNK, 11/2017-01/2019, graduated and made his diploma thesis on the project; Lilla Antal, NNK, 07/2018-02/2020, made her diploma thesis on the project and will graduate in February 2020.

BSc students:

Ilona Csordás, NNK; 05/2019-05/2020, made her diploma thesis on the project and will graduate in May 2020. Two BSc students who were not regularly employed but worked for free and the work was done as part of their compulsory practical training: Anna Orsolya Balogh, NNK, 05/2018-05/2019 and Béla Huszák, NNK, 05/2018-05/2019 graduated and made their diploma theses on the project.

1.1 Training workshops attended, student exchange within the project

Dávid Kis, Essential Molecular Biology – A hands-on laboratory course, Porto, Portugal, 01-19.07.2019. The training course provided hands-on training on a large palette of molecular biological techniques routinely applied in the work of the project, such as protein analysis, nucleic acid analysis.

Eszter Persa, Enikő Kis, Katalin Balázs, Statistical analyses of measured laboratory results, 20-21 and 27-28.11.2019., Budapest, Hungary. This course offered detailed theoretical information about certain statistical probes and also a useful practical session helping to perform a more proficient statistical analysis of LEU-TRACK data.

Rita Hargitai, Enikő Kis, Essentials of radiation leukaemogenesis, Public Health England, Didcot, UK, 20-23 January, 2020. During this LEU-TRACK-organized training course a panel of methods useful for leukaemia diagnosis not routinely applied in NNK could be learned.

Prabal Subedi, Radiation-induced effects with particular emphasis on genetics, development, teratology, cognition as well as space-related health issues, SCK-CEN, Mol, Belgium, 12-23.03.2018. Dr. Subedi is an expert on the field of proteomics. This course gave him an introduction in theory and practice to hot topics in radiation biology.

Prabal Subedi, Proteome Discoverer and Compound Discoverer user meeting, Bremen, Germany, 10.-11.12.2018. This course offered methods to improve software and analysis skills for mass-spectrometry-based data sets.

Prabal Subedi, Proteome Discoverer and Compound Discoverer user meeting, Bremen, Germany, 9.-10.12.2019. This course gave an update of methods and software tools to analyse mass-spectrometry-based data sets.

From the 10th of September to 14th of September 2018 Dr. Amir Mofidi, GUF, visited the cooperation partner NNK in Budapest, Hungary, to be trained in preparation of EVs from bone marrow and blood samples from CBA mice.

1.2 Training and other workshops organized by LEU-TRACK

The Young Scientist´s Session, European Radiation Protection Week (ERPW), Rovinj, Croatia, 5.10.2018. This workshop gave students the possibility to exercise their presentation skills in front of a large audience. We especially welcomed not only the peers but also the more experienced participants to give the presenters scientific questions, comments, and advice. Fourteen students gave a 15 min presentation each to an audience of around 60 attendees. The programme is included as **Annex 1**.

The workshop "The role of extracellular vesicles in mediating ionizing radiation-induced bystander and systemic effects" was organised as a satellite meeting to ICRR 2019, 25th August 2019. This meeting was organised together with the CONCERT project SEPARATE. The main aim of this meeting was to present recent scientific data related to the impact of ionizing radiation on EV biology and function. A further specific aim was to present the latest findings generated in the two CONCERT projects. Additionally, some international experts on this area were invited to give a presentation. The meeting was a great success with more than 200 participants. The programme is included as **Annex 2**.

The workshop "Essentials of radiation leukaemogenesis" was organised at CRCE (Public Health England, Oxfordshire, UK), 20th – 23rd January 2020. The aim of the course was to provide information about the processes behind radiation-induced acute myeloid leukaemogenesis, including the key molecular and genetic events, risk factors and modifiers of risk. Ten participants, most of them senior scientists from different institutions around Europe, attended the training course. The course consisted of a theoretical and practical part. All lecturers and supervisors were experts on the field. The program with detailed information about the course is included as **Annex 3**.

2 Dissemination

2.1 National meetings and conferences

Dávid Kis, Eszter Persa, Tünde Szatmári, Géza Sáfrány, Katalin Lumniczky: The role of bone marrow extracellular vesicles in mediating radiation-induced bystander effects: changes in the bone marrow (Csontvelői extracelluláris vezikulák szerepe a sugárzás indukálta bystander hatásban, változások a csontvelőben) – VII. Eötvözet Conference, Szeged, Hungary, 6-7 April, 2018, oral presentation

Dávid Kis, Tünde Szatmári, Eszter Persa, Géza Sáfrány, Katalin Lumniczky : Bone marrow extracellular vesicles and radiation-induced systemic effects (Csontvelői extracelluláris vezikulák szerepe a sugárzás szisztémás hatásában). XXII. Scientific Forum, Semmelweis University, Budapest, Hungary, 12-13 April, 2018, oral presentation

Dávid Kis, Eszter Persa, Tünde Szatmári, Géza Sáfrány, Katalin Lumniczky: Extracellular vesicles and their role in mediating radiation effects in the bone marrow (Extracelluláris vezikulák sugárhatás közvetítése a csontvelőben). Bolyai Conference, Eötvös Lóránd University, Budapest, Hungary, 14-15 April, 2018, oral presentation

Dávid Kis, Tünde Szatmári, Eszter Persa, Nikolett Sándor, Rita Hargitai, Enikő Kis, Géza Sáfrány, Katalin Lumniczky: Acute and chronic health effects of extracellular vesicles from irradiated mice. Molecular Life Science Conference, Eger, Hungary, 29-31 March, 2019, poster presentation

Kis Dávid, Persa Eszter, Szatmári Tünde, Sándor Nikolett, Hargitai Rita, Kis Enikő, Sáfrány Géza, Lumniczky Katalin: Short and long-term effects of extracellular vesicles in radiation-induced bystander responses. XXVII Annual Congress of the Hungarian Biophysical Society, Debrecen, Hungary, 26-29 August, 2019, oral presentation

Antal Lilla, Balázs Katalin, Kis Dávid, Mihály Judith, Persa Eszter, Sándor Nikolett, Szatmári Tünde, Lumniczky Katalin: Comparison of different methods for EV isolation from blood suitable for multiple investigations (Extracelluláris vezikulák izolálási módszereinek összehasonlítása). XXVII Annual Congress of the Hungarian Biophysical Society, Debrecen, Hungary, 26-29 August, 2019, poster presentation

Eric Rutten, Lourdes Cruz-Garcia, Katalin Lumniczky, Tünde Szatmári, Mark Hill and Christophe Badie: The role of extracellular vesicles in radiation-induced acute myeloid leukaemia. University of Oxford, Department of Oncology student symposium, 5th June, 2019, poster presentation

Eric Rutten, Lourdes Cruz-Garcia, Katalin Lumniczky, Tünde Szatmári, Mark Hill and Christophe Badie: The role of extracellular vesicles in radiation-induced acute myeloid leukaemia. PHE Student Day, 6-7th March, 2019, poster presentation

Denise Eckert: The role of extracellular vesicles in modulating the risk of low dose radiation-induced leukaemia. Goethe University, Frankfurt, 18/07/2019, oral presentation

Denise Eckert, Franz Rödel: The Role of Extracellular Vesicles in Modulating the Risk of Low Dose Radiation-induced Leukaemia: Characterization of Vesicles by FACS. 22nd annual meeting DeGBS, Mannheim, 23-25.09.2019, oral presentation

Eckert D., Subedi P, Hehlgans S., Martin D, Rödel C, Lumniczky K, Tapio S, Rödel F: Characterization of serum-derived extracellular vesicles from leukaemic patients to identify leukaemic and radiation biomarkers. DEGRO, Wiesbaden, 25.–28.6, 2020, poster presentation (planned)

2.2 International meetings and congresses

Tünde Szatmári, Dávid Kis, Eszter Persa, Rita Hargitai, Enikő Kis, Géza Sáfrány, Katalin Lumniczky: The role of extracellular vesicles in mediating radiation-induced bystander effects in the haematopoietic system. ISEV2018 (International Society for Extracellular Vesicles) annual meeting, Barcelona, Spain, 2-6 May, 2018, oral presentation

Eszter Persa, Tünde Szatmári, Nikolett Sándor, Lívia N. Naszályi, Géza Sáfrány, Katalin Lumniczky: Isolation of bone marrow extracellular vesicles for in vivo studies in mice. ISEV2018 (International Society for Extracellular Vesicles) annual meeting, Barcelona, Spain, 2-6 May, 2018, poster presentation

Tünde Szatmári, Enikő Kis, Eszter Persa, Anett Benedek, Géza Sáfrány and Katalin Lumniczky: Radiation induced bystander signals in the blood can be mediated by extracellular vesicles. RAD2018, Ohrid, Macedonia, 18-22 June, 2018, poster presentation

Dávid Kis, Eszter Persa, Tünde Szatmári, Nikolett Sándor, Rita Hargitai, Géza Sáfrány and Katalin Lumniczky: Extracellular Vesicles mediate Radiation-Induced Bystander Effects in the Bone Marrow. 44th Annual Meeting of the European Radiation Research Society, Pécs, Hungary, 21-25 August, 2018, poster presentation

Tünde Szatmári, Rita Hargitai, Enikő Kis, Eszter Persa, Nikolett Sándor, Géza Sáfrány and Katalin Lumniczky: Ionizing radiation induces AML related changes in the cargo of extracellular vesicles from blood and bone marrow. 44th Annual Meeting of the European Radiation Research Society, Pécs, Hungary, 21-25 August, 2018, poster presentation

Katalin Lumniczky, Tünde Szatmári, Eszter Persa, Dávid Kis, Nikolett Sándor, Rita Hargitai, Géza Sáfrány: The role of extracellular vesicles in mediating or mitigating ionizing radiation effects in the bone marrow. 44th Annual Meeting of the European Radiation Research Society, Pécs, Hungary, 21-25 August, 2018, oral presentation

Nikolett Sándor, Eszter Persa, Tünde Szatmári, Rita Hargitai, Róbert Deák, Judit Mihályi, Dávid Kis, Katalin Lumniczky: The effect of ionizing radiation on amount and phenotype of bone marrow-derived extracellular vesicles. 3rd ERPW, Rovinj, Croatia, 1-5 October, 2018, oral presentation

Dávid Kis, Eszter Persa, Tünde Szatmári, Nikolett Sándor, Rita Hargitai, Géza Sáfrány and Katalin Lumniczky: Extracellular vesicles from irradiated mice induced apoptosis in mouse bone marrow. 3rd ERPW, Rovinj, Croatia, 1-5 October, 2018, oral presentation

Katalin Lumniczky, Dávid Kis, Tünde Szatmári, Rita Haargitai, Eszter Persa: Extracellular vesicles contribute to the development of ionizing radiation-induced late bone marrow pathologies. ISEV Annual Meeting, Kyoto, Japan, 25-29 April, 2019, oral presentation

Tünde Szatmári, Dávid Kis, Nikolett Sándor, Eszter Persa, Rita Hargitai, Enikő Kis, Katalin Balázs, Géza Sáfrány, Katalin Lumniczky: The effect of in vivo irradiation on the extracellular vesicle's cargo and uptake. ISEV Annual Meeting, Kyoto, Japan, 25-29 April, 2019, poster presentation

Eszter Persa, Tünde Szatmári, Nikolett Sándor, Géza Sáfrány, Katalin Lumniczky: Pitfalls in isolation and characterisation of bone marrow extracellular vesicles mediating radiation-induced bystander effects in mice. Seventh International Conference on Radiation in Various Fields of Research. Herceg Novi, Montenegro, 10-14 June, 2019, poster presentation

Katalin Lumniczky: LEU-TRACK: The Role of Extracellular Vesicles in Modulating the Risk of Low Dose Radiation-induced Leukaemia – an introduction to the project. ICRR 2019: 25-29 August, 2019, oral presentation

Katalin Lumniczky: Potential involvement of extracellular vesicles in ionizing radiation induced bone marrow pathologies. ICRR 2019: 25-29 August, 2019, oral presentation

Rita Hargitai, Enikő Kis, Tünde Szatmári, Géza Sáfrány, Katalin Lumniczky: Detection of loss of Sfpi1 gene from metaphase and interphase cells of radiation-exposed mice using FISH: a technique for the diagnosis

of leukemia. European Radiation Protection Week Stockholm, Sweden, 10-14 October, 2019, poster presentation

Katalin Lumniczky, Dávid Kis, Tünde Szatmári, Eszter Persa, Rita Hargitai, Nikolett Sándor, Enikő Kis, Géza Sáfrány: The role of extracellular vesicles in ionizing radiation-induced bone marrow pathologies. International Workshop on the causes of childhood leukemia Freising, Germany, 20-22 November, 2019, oral presentation

Tünde Szatmári, Dávid Kis, Eszter Persa, Rita Hargitai, Enikő Kis, Nikolett Sándor, Katalin Balázs, Ilona Csordás, Géza Sáfrány, Katalin Lumniczky: Ionizing radiation induces AML related changes in the cargo of extracellular vesicles from haematopoietic system. International Workshop on the causes of childhood leukemia Freising, Germany, 20-22 November, 2019, oral presentation

Eric Rutten, Lourdes Cruz-Garcia, Katalin Lumniczky, Tünde Szatmári and Christophe Badie. Radiation-induced bone marrow-blood RNAs cargo modifications and potential role in leukaemogenesis, ARR 2018, June 25-27th, 2018, poster presentation

Eric Rutten, Lourdes Cruz-Garcia, Katalin Lumniczky, Tünde Szatmári and Christophe Badie: Analysis of Bone Marrow and Leukaemia Cell Extracellular Vesicle miRNA cargos. ERPW 2018: 1- 5 October, 2018, oral presentation

Eric Rutten, Mark Hill and Christophe Badie: Radiation-induced modifications to extracellular vesicle cargos in specific bone marrow cell subpopulations. ICRR 2019: 25-29 August, 2019, poster presentation

Eric Rutten, Lourdes Cruz-Garcia, Mark Hill and Christophe Badie: Radiation-induced modifications to bone marrow extracellular vesicle cargoes: methodologies and strategies. EV Workshop at ICRR 2019, 25th August 2019, oral presentation

Lourdes Cruz-Garcia, Eric Rutten, Katalin Lumniczky, Tünde Szatmári and Christophe Badie: Ionizing radiation modifies the miRNA cargo of bone marrow and plasma extracellular vesicles. 66th Annual RRS Meeting: October 2020, poster presentation (planned)

Christophe Badie: Measuring response to radiation exposure in human blood by transcriptomic technologies, ongoing studies and future approaches. Annual Columbia University radiobiology workshop 2020, oral presentation (planned)

Franz Rödel: An exosomal secretion and cellular uptake of the inhibitor of apoptosis protein Survivin modulates DNA repair capacity and apoptosis in colorectal tumor and endothelial cells. EV Workshop at ICRR 2019, 25th August 2019, oral presentation

Prabal Subedi, Omid Azimzadeh, Michael Schneider, Fabian Metzger, Stefanie Hauck, Tünde Szatmari, Katalin Lumniczky, Simone Mörtl, Mike Atkinson, Soile Tapio: Lysis buffers for mass spectrometric proteomic analyses of exosomes: Which buffer works best? ERPW, Rovinj, Croatia, 1-5 October, 2018, poster presentation

Prabal Subedi: Proteomic analyses of exosomes derived from bone marrow and blood plasma in irradiated mice. Young Scientist´s Session, ERPW, Rovinj, Croatia, 1-5 October, 2018, oral presentation

Soile Tapio: The role of extracellular vesicles in mediating ionizing radiation-induced bystander and systemic effects. ICRR 2019, Manchester, 25-29 August, 2019, oral presentation

Prabal Subedi, Dávid Kis, Rosemarie Kell, Omid Azimzadeh, Tünde Szatmári, Eszter Persa , Katalin Lumniczky, Soile Tapio: Injection of extracellular vesicles from bone marrow of irradiated mice causes proteome changes in the non-irradiated murine hippocampus. ICRR 2019, Manchester, 25-29 August, 2019, poster presentation

Prabal Subedi, Denise Eckert, Stephanie Hehlgans Franz Rödel, Michael J. Atkinson, Soile Tapio: Ionizing radiation induces changes the proteome in extracellular vesicles- possible biomarkers of radiation. Novel Proteomic Perspectives on Aging, Cancer and Disease, Seattle, USA, 8–11.03.2020, poster/oral presentation (planned)

2.3 Publications

Tünde Szatmári, Eszter Persa, Enikő Kis, Anett Benedek, Rita Hargitai, Géza Sáfrány and Katalin Lumniczky. Extracellular vesicles mediate low dose ionizing radiation-induced immune and inflammatory responses in the blood. Int J Radiat Biol. 2019 Jan;95(1):12-22. doi: 10.1080/09553002.2018.1450533

Szatmári T, Hargitai R, Sáfrány G, Lumniczky K. Extracellular Vesicles in Modifying the Effects of Ionizing Radiation. Int J Mol Sci. 2019 Nov 6;20(22). pii: E5527. doi: 10.3390/ijms20225527

Subedi P, Schneider M, Philipp J, Azimzadeh O, Metzger F, Moertl S, Atkinson MJ, Tapio S. Comparison of methods to isolate proteins from extracellular vesicles for mass spectrometry-based proteomic analyses. Anal Biochem. 2019 Nov 1;584:113390.

2.4 Project website

Research gate profile (https://www.researchgate.net/project/The-Role-of-Extracellular-Vesicles-in-Modulating-the-Risk-of-Low-Dose-Radiation-induced-Leukaemia-LEU-TRACK)

3 Annex 1.

STUDENT´S DAY ERPW 05.10.2018

Hotel Lone

8:30-8:45	Pavelic	Luka	DEVELOPMENT OF A COMPACT SiPM-BASED GAMMA AND X-RAY DETECTOR FOR DOSE RATE MEASUREMENTS
8:45-9:00	Maremonti	Erica	CHRONIC EXPOSURE TO GAMMA RADIATION INDUCES REPROTOXIC EFFECTS IN COMBINATION WITH ENHANCED GERM CELL APOPTOSIS AND DNA DAMAGE IN CAENORHABDITIS ELEGANS EMBRYONIC CELLS
9:00-9:15	Raines	Katherine	PARASITISM MEDIATES NEGATIVE EFFECTS OF RADIATION TO BUMBLEBEES AS DEMONSTRATED BY LABORATORY EXPERIMENTS AND FIELD STUDIES IN CHERNOBYL
9:15-9:30	Beaumont	Tiffany	PERSONALIZED RADIOIODINE UPTAKE MEASUREMENT WITH GAMMA-CAMERA USING 3D REALISTIC THYROID PHANTOMS
9:30-9:45	Gómez Polo	Francisco	TRANSFER PARAMETERS VALUES FOR 90SR AND 137CS ISOTOPES IN MEDITERRANEAN ECOSYSTEM
9:45-10:00	García Puerta	Blanca	ENHANCE THE DECISION-MAKING PROCESS TO MINIMIZE THE IMPACT IN AGRICULTURAL AREAS DERIVED FROM A NUCLEAR ACCIDENT
10:00-10:15	Virgili	Nicole	VERIFYING THE PERFORMANCE OF THE ARGON-41 MONITORING SYSTEMFROM FLUORIDE-18 PRODUCTION FOR MEDICAL APPLICATION
10:15-10:30	Justic	Mihaela	CONSTRUCTION OF THE MAMMOGRAPHY PHANTOM FOR 2D AND 3D X-RAY IMAGING
10:30-11:00	COFFEE		
11:00-11:15	Sándor	Nikolett	THE EFFECT OF IONIZING RADIATION ON AMOUNT AND PHENOTYPE OF BONE MARROW-DERIVED EXTRACELLULAR VESICLES
11:15-11:30	Subedi	Prabal	PROTEOMIC ANALYSES OF EXOSOMES DERIVED FROM BONE MARROW AND BLOOD PLASMA IN IRRADIATED MICE
11:30-11:45	Kis	Dávid	EXTRACELLULAR VESICLES FROM IRRADIATED MICE INDUCED APOPTOSIS IN MOUSE BONE MARROW
11:45-12:00	Nisar Khan	Zohaib	"SEPARATE": SYSTEMIC EFFECTS OF PARTIAL-BODY EXPOSURE TO LOW RADIATION DOSES
12:00-12:15	Mafodda	Alessia	EXTERNAL DOSE-RATE MEASUREMENTS BASED ON SMARTPHONE CMOS SENSORS

12:00-12:15	Mafodda	Alessia	EXTERNAL DOSE-RATE MEASUREMENTS BASED ON SMARTPHONE CMOS SENSORS
12:15-12:30	Dressel	Tobias	NANODOSIMETRIC ESTIMATION OF DNA DAMAGE IN A GOLD NANOPARTICLE LOADED CELL AFTER PHOTON IRRADIATION
12:30-13:30	LUNCH		

4 Annex 2.

The role of extracellular vesicles in mediating ionizing radiation-induced bystander and systemic effects

This satellite meeting is supported by the CONCERT project that has received funding from the EURATOM research and training programme 2014-2018 under grant agreement No 662287.

http://www.concert-h2020.eu/;

https://sites.google.com/view/separate-project/home

Extracellular vesicles (EVs) are key mediators of intercellular communication both under physiological conditions and in a wide range of pathologies. Recent studies have shown the role of EVs in mediating radiation-induced bystander and systemic effects. The main aim of this satellite meeting is to present recent scientific data related to the impact of ionizing radiation on EV biology and function.

In the frame of the EURATOM-funded CONCERT project two research projects (LEU-TRACK and SEPARATE) specifically investigate the role of EVs in mediating radiation-induced bystander effects. LEU-TRACK focusses on the role of blood and bone marrow-derived EVs in mediating radiation-induced leukaemogenesis. SEPARATE investigates exosomes from exposed tissues, and their specific bioactive cargo, for their role in mediating out-of-target effects *in vitro* and *in vivo*. A further specific aim of this satellite meeting is to present latest findings generated in these two projects.

Sunday – 25.08.2019, 10:00 – 13:30, Room Charter 4

Chair: Soile Tapio
Co-chair: Katalin Lumniczky

10:00 – 10:10 Welcome and introduction
Soile Tapio

10:10 – 10:20 LEU-TRACK: The Role of Extracellular Vesicles in Modulating the Risk of Low Dose Radiation-induced Leukaemia – an introduction to the project
Katalin Lumniczky

10:20 – 10:40 The SEPARATE project: origin and perspectives
Mariateresa Mancuso

10:40 – 11:00 Exosome signalling roles in the non-targeted effects of radiation: investigating tissue and organ dependence
Munira Kadhim

11:00 – 11:20 Radiation-induced cargo modifications in specific bone marrow cell subpopulations
Eric Rutten

11:20 – 11:40 Potential involvement of extracellular vesicles in ionizing radiation induced bone marrow pathologies
Katalin Lumniczky

11:40 – 12:00 **Coffee break**

12:00 – 12:20 Exosomal secretion and cellular uptake of the inhibitor of apoptosis protein Survivin modulates DNA repair capacity and apoptosis in colorectal tumor cells
Franz Rödel

12:20 – 12:40 Exosomes from irradiated peripheral blood mononuclear cells suppress apoptosis in recipient cells
Simone Mörtl

12:40 – 13:00 Extracellular Vesicles are Informative of Cranial Irradiation Exposure Induced Inflammatory Phenotype
Amrita K Cheema

13:00 – 13:20 Extracellular Vesicles as a Novel Therapy for Radiation-Induced Cognitive Dysfunction
Charles Limoli

13:20 – 13:30 Concluding remarks
Soile Tapio, Katalin Lumniczky

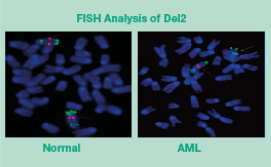
5 Annex 3.

Public Health England

20th - 23d January 2020

Essentials of Radiation Leukaemogenesis

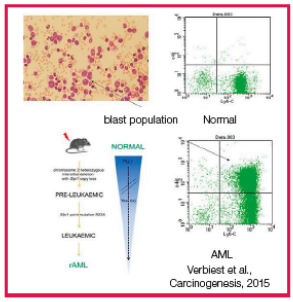
Organised by the CONCERT LEU-TRACK consortium and hosted by PHE, this course aims to cover the core concepts in the study of radiation leukaemogenesis, including use of state-of-the art model systems and analytical methods



Centre for Radiation, Chemical & Environmental Hazards, Public Health England, Didcot, Oxfordshire, OX11 ORQ, United Kingdom

Topics to be covered

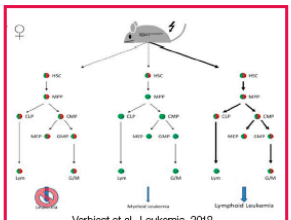
- murine models of radiation-induced leukaemia
- cytogenetic approaches and key molecular events
- physical radiation dosimetry
- importance of radiation quality
- target cells and post-irradiation metabolism
- recombination mediated translocation pathways
- new models for research
- extracellular vesicles and leukaemia
- relevance to human studies
- medical exposure as a risk factor
- epidemiology



Organising Committee

Dr Christophe Badie
Cancer Mechanisms and Biomarkers Group Leader, Radiation Effects Department

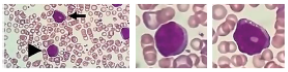
Dr Rosemary Finnon
Cancer Mechanisms and Biomarkers Group, Radiation Effects Department



Practical Sessions

Demonstrations will be provided on essential techniques, such as:

- leukaemia diagnosis in mouse models – dissection techniques and haematopoeitic tissue harvesting, blood smear preparation and differential counts, characterisation of leukaemic blast cells with immunophenotyping
- analysis of rAML-associated chromosomal aberrations with cytogenetic techniques such as FISH



Nucleated blastic cells in leukaemic mouse. Verbiest et al., Leukemia, 2018.

Speakers

Dr Simon Bouffler
Head of Radiation Effects Department, PHE

Dr Jonathan Eakins
Physical Dosimetry, PHE

Dr Christophe Badie
Cancer Mechanisms and Biomarkers Group Leader, PHE

Dr Michele Ellender
Cytogenetics & Pathology Group, PHE

Michael Gillies
Radiation Epidemiology Group, PHE

Melis Karabulutoglu
Cancer Mechanisms and Biomarkers Group, PHE

Eric Rutten
Cancer Mechanisms and Biomarkers Group, PHE

Grainne O'Brien
Cancer Mechanisms and Biomarkers Group, PHE

Dr Lourdes Cruz Garcia
Cancer Mechanisms and Biomarkers Group, PHE

Roisin McCarron
Cancer Mechanisms and Biomarkers Group, PHE

Dr Serge Candeias
CEA, France

Dr Rosemary Finnon,
Cancer Mechanisms and Biomarkers Group, PHE

Tünde Szatmári,
OSSKI, Hungary

Who can apply?

The course is open to MSc and PhD students as well as Post-Doctoral scientists. Preference will be given to those registered with an EU university or working in an EU country.

Course fee:
None. Travel costs need to be paid for by applicant.

Accommodation and food provided for up to 12 participants.

Application

Required documents:

- letter of motivation and CV
- supporting letter from the supervisor/head of laboratory (students only)

For applications and further details, please email christophe.badie@phe.gov.uk or call +44(0)1235825088

Application deadline: 30.09.2019

Additional information:

A social event for attendees will be organised – details provided at a later date.

For updates check:
http://www.concert-h2020.eu/en/Events

CONCERT GA 662287

Essentials of Radiation Leukaemogenesis

Organised by the Cancer mechanisms and biomarkers group, at CRCE (Public Health England, Oxfordshire, UK), 20th – 23rd January 2020.

The Course was designed to provide insight into the processes behind radiation-induced acute myeloid leukaemogenesis, including the key molecular and genetic events, risk factors and modifiers of risk, and in vivo model systems. The topics included in the course were the followings:

- Aetiology of rAML – including risk factors, potential modifiers and uncertainties in modelling risk at low doses/doe rates
- Haematopoietic stem/progenitor cells as target cells for rAML, measuring HSPC radio sensitivity and identifying pre-leukaemic changes
- Animal models of rAML
- Radiation dosimetry – internal and external
- Epidemiology

Practical:

- E block animal unit – including bone marrow dissection and cell prep
- HSPC harvest and culture
- Immunophenotyping of AML samples
- FISH/CGH and molecular methods of mutation/aberration detection
- Differential counts
- Pathology findings
- Pyrosequencing analysis
- Gene expression
- Flow cytometry

The course included 13 speakers from Public Health England and an invited speaker from the CEA (France). The list of the speakers is presented below.

1.) **Dr Simon Bouffler** - Head of Radiation Effects Department, PHE
   - Introduction and historical perspective

2.) **Dr Jonathan Eakins** - Physical Dosimetry, PHE
   - External Dosimetry: This lecture explains the basic principles of radiation dosimetry, with a focus on the various quantities used for assessing exposures external to the body. Three types of dose quantity will be presented: primary quantities, protection quantities, and operational quantities, with discussions on why each of these are required, how they complement and interrelate with one another, and how they can be evaluated and measured.

3.) **Dr Christophe Badie** - Cancer Mechanisms and Biomarkers Group Leader, PHE
   - Transgenic Sfpi-1/Pu.1 reporter models of rAML: This short presentation will describe more specifically a new model which has been developed in the laboratory to track live pre-leukaemic cells in vivo, the monitoring of clonal expansion and the new insights obtained on radiation leukaemogenesis

4.) **Michael Gillies** - Radiation Epidemiology Group, PHE
   - Leukaemia and Radiation – some of the epidemiological evidence: This talk includes details of the history of radiation induced leukaemia and the first cases reported, as well as A-bomb survivor and radiation worker studies.

5.) **Melis Karabulutoglu** - Cancer Mechanisms and Biomarkers Group, PHE
   - HSCs and Metabolism. Melis joined Cancer Mechanisms and Biomarkers group as a DPhil student (Jan 2018) under supervision of Dr Christophe Badie on a joint degree programme with the University of Oxford. Her project mainly focuses on investigating the mechanisms of radiation leukaemogenesis, characterisation of haematopoietic stem cells and modulation of risk. In this particular lecture Melis will focus on the importance of metabolism in regulating hematopoietic homeostasis under normal and following exposure to external stress e.g. Ionising radiation is of significant interest in radiation protection and public health fields

6.) **Eric Rutten** - Cancer Mechanisms and Biomarkers Group, PHE
   - Extracellular vesicles: hidden messengers of leukaemia: Extracellular vesicles were long considered as a cell's garbage disposal, but are now thought to instead be an intracellular courier service. Can leukaemia hijack this system, and how important is it in leukaemogenesis?

7.) **Grainne O'Brien** - Cancer Mechanisms and Biomarkers Group, PHE
   - Genetic and epigenetic consequences of radiation exposure in human and mouse leukaemogenesis

8.) **Dr Lourdes Cruz Garcia** - Cancer Mechanisms and Biomarkers Group, PHE
   - Pyrosequencing: A lab-based demonstration of the DNA sequencing using light detection procedure

9.) **Roisin McCarron** - Cancer Mechanisms and Biomarkers Group, PHE
   - A new murine model hypersensitive to rAML: This talk covers CRCEs novel mouse model, developed to inherit an engineered Sfpi.1/pu.1 point mutation, to investigate the effects of the mutation on radiation induced acute myeloid leukaemia hypersensitivity.

10.) **Dr Serge Candeias** - CEA, France.
   - Ionizing radiation effects on the control of V(D)J recombination fidelity in mice: B and T lymphocytes are unique in that they need to assemble the genes coding for their antigen receptors from discrete V, D and J genes before they are expressed. This somatic rearrangement is mediated by the RAG recombinase that specifically targets immunoglobulin and T-cell receptor genes and requires functional NHEJ DNA repair activity. However, it is now well established that mis-controlled V(D)J recombination can be involved in translocations found in lymphoid malignancies. I will present our recent work addressing the influence of ionizing radiation on V(D)J recombination in mice.

11.) **Dr Rosemary Finnon** - Cancer Mechanisms and Biomarkers Group, PHE
   - Radiation-induced leukaemogenesis, introduction and background

12.) **Paul Finnon** – Cancer Mechanisms and Biomarkers Group, PHE
   - Safety and Security information at CRCE

13.) **James Marsh** – Physical dosimetry, PHE
   - Internal Dosimetry: This lecture explains the principle of internal dosimetry following intakes of radionuclides into the body. It focuses on those nuclides that preferentially deposits in the skeleton which may lead to bone cancer or leukaemia. It explains why certain nuclides are more likely to induce leukaemia.

Ten participants attended the training course from different institutions around Europe: Military Medical Academy (Sofia, Bulgaria), Oxford Brookes University (Oxford, UK), Ghent University (Belgium), WITS University (South Africa), National Centre of Radiobiology and Radiation Protection (Sofia, Bulgaria), Division of Radiobiology and Radiohygiene of the National Public Health Centre (Budapest, Hungary) and Laboratory of Experimental Radio toxicology and Radiobiology at the Institute of Radioprotection and Nuclear Safety (France). The participants bio sketches are included below:

1.) **Dr Galina Racheva:** Dr. Galina Racheva, finished her PhD degree in Radiobiology at Military Medical Academy, Sofia, Bulgaria in February 2015. She has since been a senior professor assistant in the Laboratory of Radiation protection and Radiobiology. Her focus is on cytogenetic radiation-induced effects. The theme of the PhD thesis is "Effects of innovative immunomodulatory

molecules as a part of the complex scheme of the Acute Radiation Syndrome treatment in therapeutic and experimental exposure". She researched the radiation protection activity of two main natural amino acids (betaine and N-acetyl-L-cysteine) applied to in vitro model systems of lymphocytes isolated of peripheral blood. She has a master's degree in "Genetic and cellular engineering" (Sofia University "St. Kliment Ohridski, Sofia, Bulgaria). She was on a fellowship in Royal Free Hospital (London, UK) in the laboratory of Cytogenetic for 6 months, as a part of her master's degree plan. She has certificates of different specializations in Radiation dosimetry, cytogenetic and epidemiology by Bulgarian institutions and abroad. With the research results she has attended the international conference of "Radiation protection in Medicine" (Bulgaria) few times, in the international conference of the 11th International Symposium on Chromosomal Aberrations ISCA11 (Greece), other international congresses, conferences, workshops, etc. Her focus of the current research is to determine the carcinogenic risk of oncology patients who pass radiation therapy and diagnostic procedures with irradiation. One of the main tasks in front of her is to determine the risk of development of secondary radiation effects such as radiation-induced leukaemia.

2.) **Milena Yoncheva:** Milena is a PhD-student and professor assistant in the Laboratory of Radiation Protection and Radiobiology, Military Medical Academy, Sofia, Bulgaria. Her supervisor of the PhD-project is Professor Mitko Alyakov, MD, PhD in Radiobiology. She continues with the research of the natural metabolites as potential radio protectors. She focusses on the research of the antioxidants N-acetyl-L-Cysteine and £-Lipoic acid as potential radioprotectors. She is interested in the research of the risk of development of secondary radiation effects such as radiation-induced leukaemia.

3.) **Dr Seda Tuncay-Cagatay:** Dr. Seda Tuncay Cagatay obtained her PhD in Cancer Biology from Middle East Technical University (METU), Turkey in 2014 under the supervision of Professor Sreeparna Banerjee, during which she was also appointed as research & teaching assistant by the Department of Biological Sciences, METU. During her MSc and PhD studies, she studied on functional characterization of several cancer-related genes in colorectal cancer. Then she worked as a postdoctoral researcher in Baskent University, in Turkey. She then moved to the UK where she joined Professor Munira Kadhim`s Genomic Instability and Cell Communications research group in Oxford Brookes University. Currently, she works on a project investigating exosome-mediated radiation signalling between tissues and underlying mechanisms after partial or whole-body radiation exposures.

4.) **Dr Maryam Ahmadi:** Dr. Maryam Ahmadi obtained her PhD in Cancer Research from University of Dundee, Scotland under supervision of Dr. David Meek. Her PhD thesis is titled inhibition of PLK1 by p53 and by PLK1 targeted drugs. Prior to her PhD, she completed a master's degree in Cancer Pharmacology at the Institute of Cancer Therapeutics, University of Bradford. She then worked as a Research Assistant in Prof. Roger Phillips group at the same institute investigating the effect of hypoxia on the activity of anti-cancer drugs. Dr. Ahmadi is now a Post-Doctoral Research Assistant in the Genomic Instability and Cell Communications group (Prof. Munira Kadhim laboratory) at the Oxford Brookes University working on the effect of low-dose ionising radiation on the development/progression of cataract.

5.) **Prof. Ans Baeyens:** Prof. Ans Baeyens graduated as a Master of Science in bio-engineering in 2000 and obtained her PhD in radiobiology in 2005 at Ghent University. She lived in South Africa from 2005 until 2015 where she started a Radiobiology lab at the University of the Witwatersrand (WITS) in Johannesburg. She supervised 14 post graduate students in radiobiology projects and was awarded several research grants in South Africa (MRC, CANSA, NRF). Since October 2015, she joined Ghent University as a tenure track professor at the faculty of Health Sciences. Currently she combines this position with the joint position at WITS University. Her research deals with chromosomal radio sensitivity of breast cancer, cervical cancer and HIV positive patients. A second focus of her research is biological dosimetry and measuring DNA damage induced by exposure to ionizing radiation. Recently, since 2017, she started a third research line on proton irradiation and hematopoietic stem and progenitor cells (HSPCs). She is (co)author of 35 publications in peer-reviewed journals and is currently promotor of 5 PhD students. She is head of the reference lab for radio sensitivity testing in Belgium. She is lecturing Physics at the faculty of Medicine and health Sciences at UGent and Radiobiology at WITS University in Johannesburg.

6.) **Simon Sioen:** PhD student - Department Human Structure and Repair Radiobiology group Ghent University, Belgium. Simon Sioen graduated in Biomedical Sciences at Ghent University in June 2018. In his thesis year, he chose a radiobiology masters dissertation, in the major 'Medical Radiation Sciences', that handled hematopoietic stem cells and progenitor cells exposed to X-rays. His interest in both physics and biology led him to continue this research as a PhD student, where he now investigates the DNA damage response in HSPCs after X-ray and proton exposure.

7.) **Dr Nevena Aneva:** Nevena is a biologist at the National Centre of Radiobiology and Radiation Protection, Sofia, Bulgaria, where she analyzes biological effects of ionizing radiation on a variety of cells, using different experimental methods like ELISA, Comet Assay, Spectroscopic methods for detection of cell viability etc. Nevena has a PhD thesis "Radiation induced inflammation" in Radiobiology, focused on radiation induced changes in inflammatory status of nuclear power plant workers, professionally exposed to low-doses of ionizing radiation. Nevena enjoys dancing salsa, reading fantasy books and make decoupage boxes in her spare time.

8.) **Dr Rita Hargitai:** Rita Hargitai graduated from Eötvös Loránd University (Budapest, Hungary) with a MSc degree in Biology in 2002 and obtained a PhD in Biology (Ecology) in 2006. She worked as a senior lecturer at the Institute of Environmental Sciences of the College of Nyíregyháza for 4 years. Between 2012 and 2016, she worked as a post-doctoral research fellow at the Department of Systematic Zoology and Ecology of Eötvös Loránd University, during which time she conducted behavioural ecology studies with songbirds. She has been working at the Department of Radiation Medicine of the Division of Radiobiology and Radiohygiene of the National Public Health Centre in Budapest as a research fellow since September 2016. Here, her first research topic was to test whether hair samples were suitable biomarkers of low-dose local ionising radiation. She studied with qPCR method the lesions and deletions of mitochondrial DNA isolated from mouse and human hair bulb samples. In 2018, she joined the CONCERT LEU-TRACK project related to the involvement of extracellular vesicles (EVs) in radiation-induced murine acute myeloid leukaemia. Her research focuses within this project are the development of a FISH technique that is able to

detect Sfpi1 deletion both in interphase and metaphase cells, and the evaluation whether EVs could mediate their bystander effects by inducing oxidative stress in the recipient cells. She also participates in the bio dosimetry tasks of assessing the radiation dose received from human blood samples performing two types of methods: dicentric chromosome analysis and micronucleus assay

9.) **Enikő Kis:** Enikő Kis graduated from the Faculty of Biology and Geology of Babes-Bolyai University (Cluj-Napoca, Romania), with MSc degree in biology in 2000. She is a PhD candidate of the National University of Public Service (Doctoral School of Military Engineering, Program of Disaster Management). She has been working at the Department of Radiation Medicine of the Division of Radiobiology and Radiohygiene of the National Public Health Centre in Budapest, Hungary, as a researcher since February 2002. Here, her first research topic was the development of a radiation sensitivity biomarker from blood cells or fibroblasts of cancer patient treated with radiation therapy by the means of comet assay, micro-array experiments and qPCR. She also studied radiation response in tissue samples (mRNA expression changes and DNA promoter methylation) and blood plasma (protein level changes) of HNSCC patients. In 2018, she joined the CONCERT LEU-TRACK project related to the involvement of EVs in murine rAML. Her research focuses within this project are the development of a FISH technique able to detect Sfpi1 deletion both in interphase and metaphase cells and the detection of chromosomal changes in the background of leukaemogenesis by G-banding technique. She has contributed to bio dosimetry investigations and international inter comparisons since 2012.

10.) **Dr Dmitry Klokov**: PhD in Radiobiology (2000, Moscow State University), currently he is the Head of the Laboratory of Experimental Radio toxicology and Radiobiology at the Institute of Radioprotection and Nuclear Safety in France. He also holds an Adjunct Professor position at the Department of Biochemistry, Microbiology and Immunology of University of Ottawa. Until recently he led a Radiobiology section at Canadian Nuclear Laboratories. His research interests lie broadly in various areas of Low-Dose Radiobiology, with an overarching goal to understand a chain of events after exposure that connects early genotoxic changes with subsequent health related tissue outcomes, such as cancer.

The program of the training course was as follows:

Programme:

Monday

3.30pm	Arrival – sign in/collect security passes (Refreshments)		Reception
4.00pm	Safety and Security information at CRCE	Paul Finnon	A2.02
4.10pm	Introduction and historical perspective	Simon Bouffler	A2.02
4.30pm	Radiation-induced leukaemogenesis – introduction and background	Rosemary Finnon	A2.02
5.10pm	Building and laboratory tour		-
6.00pm	End – passes returned to reception		Reception
6.30pm	Dinner – RAL (optional)		RAL

Tuesday

9.00am	Arrival – sign in/collect security passes		Reception
9.10am	External Dosimetry	Jonathon Eakins	A2.02
9.50am	Internal Dosimetry	James Marsh	A2.02
10.25am	Transgenic Sfpi-1/Pu.1 reporter models of Radiation induced Acute Myeloid Leukaemia	Christophe Badie	A2.02
11.00am	Tea/Coffee break		A2.02
11.30am	HSCs and Metabolism	Melis Karabulutoglu	A2.02
12.00am	Extracellular vesicles: hidden messengers of leukaemia	Eric Rutten	A2.02
12.30pm	Lunch – RAL*		A2.02
1.30pm	**Practical demonstrations**: E-Block tours + dissection procedure		E-Block
3.00pm	Tea/Coffee break		A2.02
3.15pm	**Practical demonstration**: Immunophenotyping, CGH, Pathology.		C1
5.00pm	End – Passes returned		Reception

Wednesday

9.00am	Arrival – sign in/collect passes		Reception
9.15am	SPM mouse - A New Murine Model hypersensitive to rAML	Roisin McCarron	Board Room
9.30am	Leukaemia and Radiation – some of the epidemiological evidence	Michael Gillies	Board Room
10.00am	Genetic and epigenetic consequences of radiation exposure in human and mouse leukaemogenesis	Grainne O'brien	Board Room
10.30	Tea/Coffee Break		Board Room
11.00am	**Practical demonstrations**: Bone crushing + bone marrow prep	Melis, Eric	E-Block
1.00pm	Lunch		Board Room
2.00pm	Oxford tour + turf tavern drink		Oxford
7.00pm	Dinner – A Lebanese restaurant*		Oxford

Thursday

9.00am	Arrival – Sign in/collect passes		Reception
9.15am	Ionizing radiation effects on the control of V(D)J recombination fidelity in mice	Serge Candeias	A2 .02
10.00am	Tea/coffee break		A2.02
10.20am	Pyrosequencing (practical/computer results)	Lourdes CruzGarcia	C1
11.00am	**Practical demonstrations** – Flow sorting, qPCR	Paul, Grainne	C1
12.30pm	Lunch		A2.02
1.30pm	End – sign out, travel		Reception

Animal unit tour at CRCE.

Lectures during the training course at CRCE.

Dr Christophe Badie lecturing during the training course at CRCE.