AIR² Access to INFRASTRUCTURES for Radiation protection Research

Special Issue 9

April 2020

Editorial

In this newsletter you will zoom in on the results of the LEU-TRACK project. It was a real race against the clock that this project won. The end of the project was scheduled for March 31, the date on which many of our colleagues were confined. But this unprecedented period of confinement fighting COVID-19 leaves those who are not in the front line and may be teleworking, plenty of time for reflection, writing and reading. I hope that you will take the time to read in detail this newsletter, which addresses a new topic in radiobiology: Extracellular vesicles (EVs), which are key compounds for intercellular communication. The project focuses on EVs and the hematopoietic system. The work combined mouse models and samples from leukaemic patients.

Enjoy reading, take care of yourselves and remain safe. **Dr Laure Sabatier, CEA**

The floor to...

LEU-TRACK (The role of extracellular vesicles in modulating the risk of radiation-induced leukaemogenesis) is a collaborative project between three European radiation protection research institutes, members of MELODI and/or EURADOS and a university, with a duration of 30 months (01/10/2017-31/03/2020) and a total budget of 1,335,922 €, out of which 921,786 € EC contribution.

LEU-TRACK – The role of extracellular vesicles in modulating the risk of low-dose radiation-induced leukaemogenesis

The project targets a key priority in low dose radiation research, namely basic mechanisms leading to carcinogenesis and evaluation of health risks attributable to low dose exposures. Our major objective was to study basic mechanisms in low dose radiation-induced leukaemia by focusing on the role of crosstalk between the bone marrow microenvironment and the stem cell compartment in initiating the leukemic process. The project investigated mechanisms and pathways how extracellular vesicles (EVs) (important vehicles of intercellular communication) influenced radiation-induced bone marrow damage and the development of leukaemia.

The project is structured in four work packages, three scientific and one administrative, including also tasks related to education, training and dissemination activities.

The major achievements of the project can be summarized as follows:

- We showed that ionizing radiation effects can be mediated by EVs in the haematopoietic system.
- We demonstrated that bone marrow changes caused by EVs originating from low dose irradiated mice were often similar albeit milder or less consistent to alterations induced by EVs from high dose irradiated mice.
- Although the direct role of EVs in modifying leukaemia incidence awaits further confirmation based on definitive data, it is clear that has a role in inducing bone marrow abnormalities.
- The expression of certain miRNAs in bone marrow-derived EVs are dose dependent.
- The project elucidated the importance of the EV isolation method for different biological endpoints.
- An international training course was organised on radiation leukemogenesis.
- The major topics of the project as well as recent advances in radiation-related EV research were presented at a satellite meeting during the ICRR 2019, Manchester, UK, 25-29 August 2019.

The LEU-TRACK consortium

LEU-TRACK Coordinator
Katalin Lumniczky, Unit Head, Unit of Radiation Medicine, National Public Health Institute, Budapest, Hungary

Photo: M. Birschwilks

This project has received funding from the Euratom research and training programme 2014-2018 under grant agreement No 662287

CONCERT CORNER

Future events:

28 Sept.-2 Oct. 2020
ERPW 2020, Estoril, Portugal
Extended deadline for abstract submission: 30 April

WP 6 News:

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Project coordination

This work package included 4 tasks out of which Task 2 and 3 were devoted to dissemination activities as well as education and training. Here we would like to focus on these two tasks.

Altogether, 39 conference presentations were prepared and presented by project partners at 10 different national and 13 different international meetings. Importantly, a focus was placed to disseminate project results outside the radiation research community as well, which led to poster and oral presentations at the annual meetings of the International Society for Extracellular Vesicles and at national and international cancer conferences. So far, project results were published in three scientific papers and further three joint papers are in preparation.

Photo: PHE

1) Group photo of participants at the training course organized at PHE on Essentials of Radiation Leukaemogenesis

Undoubtedly, the most important dissemination activity was the satellite meeting organized during the International Congress on Radiation Research in Manchester, UK, 25-29 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.

Photo: NNK

Katalin Lumniczky

Project-related E&T activities included the academic education of two PhD students, two MSc students and three BSc students partly financed by the project. Young scientists participated at national and international training courses on diverse topics such as basic molecular biology techniques, proteomic and mass spectrometry data set and statistical analysis, as well as radiobiology.

Two educational events were specifically initiated and/or organised by the project. The Young Scientist´s Session during the European Radiation Protection Week (ERPW), Rovinj, Croatia, 5.10.2018 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 training course “Essentials of radiation leukaemogenesis” was organised at CRCE (Public Health England, Oxfordshire, UK), 20-23 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 which consisted of a theoretical and practical part.

Photo: PHE

2) Brochure of the training course organized at PHE on Essentials of Radiation Leukaemogenesis

Extracellular vesicles mediate low dose ionizing radiation-induced immune and inflammatory responses in the blood, Szatmári T., Persa E., Kis E., Benedek A., Hargitai R., Sáfrány G., Lumniczky K. (2019), Int J Radiat Biol, 95 (1), 12-22

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

NEMZETI NÉPEGÉSZSÉGÜGYI KÖZPONT

ID Card:

Keywords:
Radiation-induced leukaemia, extracellular vesicles

Work Package leader:
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Partners:
- NNK, Hungary
- PHE, United Kingdom
- HMGU, Germany
- GUF, Germany

Duration:
30 months
(01/10/2017-31/03/2020)

Total budget:
1,335,922 €

Project website:
https://www.researchgate.net/project/The-Role-of-Extracellular-Vesicles-in-Modulating-the-Risk-of-Low-Dose-Radiation-induced-Leukaemia-LEU-TRACK

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Related to:
MELODI

The impact of EVs on leukaemia risk and characterisation of radiation effects on EV phenotype and cargo

The major objective of this work package was to investigate whether EVs from irradiated mice can transmit signals that modify the risk of leukaemia development in recipient animals and whether EV-related molecular markers can serve as biomarkers of exposure and/or disease. CBA mouse strain was used, which develops acute myeloid leukaemia upon irradiation only. The work package was structured in 6 tasks.

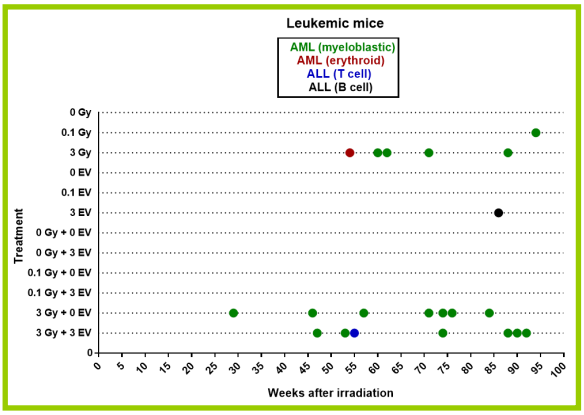


Photo: NNK

1) Development of leukaemia in mice treated with IR and/or EV injection. Dots represent individual cases of leukaemia.

Within Task 1 CBA mice were total-body irradiated with 0.1 or 3 Gy at NNK. Part of the mice were followed up in long term for leukaemia development. Bone marrow-derived EVs were isolated from another part of the mice and injected intravenously into naïve or irradiated mice.

Task 2 focused on murine sample collection and distribution to partners. Bone marrow-derived and plasma EVs were distributed to PHE (miRNA cargo analysis), HMGU (proteomic analysis), NNK and GUF (phenotypical analysis, *in vitro* and *in vivo* performed mechanistic studies).

Task 3 focused on long-term follow up of the animals to monitor the influence of EVs on leukaemogenesis. Currently approx. 50% of the mice have been euthanized either because they were ill or reached the age of 24 months and are being investigated for leukaemia diagnosis. Figure 1 shows the number of already confirmed cases of leukaemia. Our preliminary results indicate that 9.8% of mice treated with 3 Gy, 10% of mice treated with 3 Gy + 3 Gy EV and 16% of mice treated with 3 Gy + 0 Gy EV have developed AML. Until now, 1 mouse irradiated with 0.1 Gy had AML (1.1%) and no AML case was detected in solely EV treated or control mice.

Photo: PHE

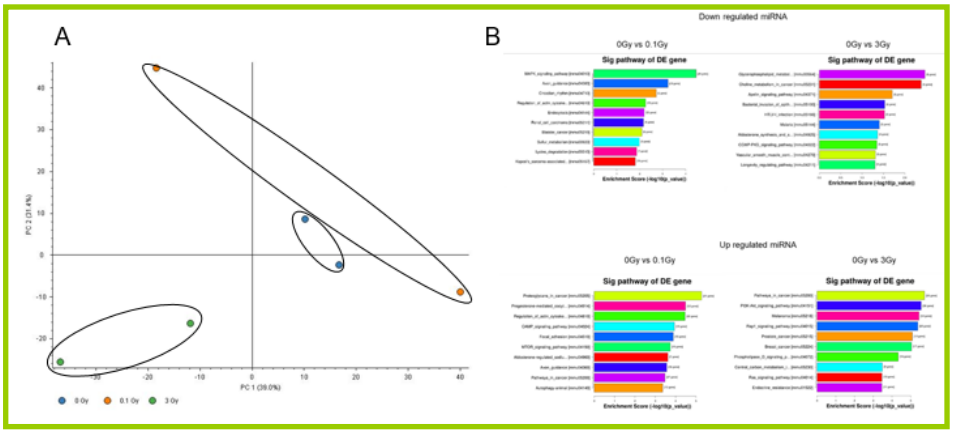
Christophe Badie

Task 4 analysed phenotypical changes of irradiated EVs. Most EVs expressed integrins typical for mesenchymal stem cells (MSCs), thus MSCs seem to release the most EVs into the BM microenvironment. Decreasing of MSC-derived EVs after irradiation was consistent with the reduction of live MSC pool in the BM.

Task 5 investigated miRNA cargo of EVs. Analysis of the bone marrow EVs from the 0.1 Gy group revealed 4 significantly upregulated miRNAs involved in the regulation of endocytosis, cell cycle, MAPK signalling, ubiquitin-mediated proteolysis, leukocyte transendothelial migration, regulation of actin cytoskeleton and adherens junction pathways. BM EVs from 3 Gy irradiated mice showed 20 miRNAs significantly deregulated. The 0.1 Gy response was conserved in 3 Gy. All miRNAs had a higher fold change at 3 Gy when compared to 0.1Gy, suggesting a dose-dependent upregulation, rather than an on/off mechanism of upregulation (Figure 2).

Task 6 investigated protein cargo of EVs. In the BM-derived EVs from mice treated with 0.1 Gy or 3 Gy, 148 and 152 proteins (Figure 2), while in the serum-derived EVs 91 and 106 proteins were deregulated, respectively. At both IR doses in both EV types there were 15 common differentially regulated proteins representing proteins responding to stress or stimulus or participating in the cellular defence.

Photo: HMGU and PHE



2) Changes in EV cargo after irradiation. A: Principal component analysis (PCA) of bone marrow EVs from sham-irradiated mice (0 Gy) and irradiated mice (0.1 Gy and 3 Gy) based on protein abundances. B: Top 10 significant pathways of the gene targets of the downregulated and upregulated miRNAs.

Radiation-induced modifications to extracellular vesicle cargos in specific bone marrow cell subpopulations, Rutten E. et al., ICRR 2019, 25-29 August 2019, conference presentation

Ionizing radiation induces AML related changes in the cargo of EVs from haematopoietic system, Szatmári T. et al., International Workshop on the causes of childhood leukemia Freising, 20-22 November 2019, conference presentation

Public Health England

ID Card:

Keywords:
Extracellular vesicles, miRNA, proteomics, EV phenotype, radiation-induced leukaemia

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Partners:
- PHE, United Kingdom
- NNK, Hungary
- HMGU, Germany
- GUF, Germany

Infrastructures:
Exposure platform:
PXI small animal irradiator, Small Animal Radiation Research Platform (SARRP)
Analytical platforms:
HELMHOLZ proteomic core facility, Nanostring, cytoflex flow cytometer
Models and tools:
CBA mouse

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Mechanistic studies investigating the role of EVs in mediating the communication between the different cells of the haematopoietic system: local and systemic effects

The objectives of this work package were to determine which cells of the peripheral haematopoietic system and bone marrow (BM) are taking up BM-derived extracellular vesicles (EVs) and how this affects BM and spleen in terms of DNA damage, oxidative stress, senescence, and global methylation. The EVs used in these studies were isolated from the BM of control mice (no irradiation) or from mice receiving total body X-ray radiation at doses of 0.1 Gy, 0.25 Gy or 2 Gy and all results were compared to directly irradiated mice using the same doses. The different BM-derived EVs were characterised by proteome and miRnome analyses (described in WP2). The changes in the proteomes of the non-irradiated BM receiving different types of EVs (bystander) compared to those of directly irradiated BM were analysed by global proteomics (work ongoing).

Photo: HMGU

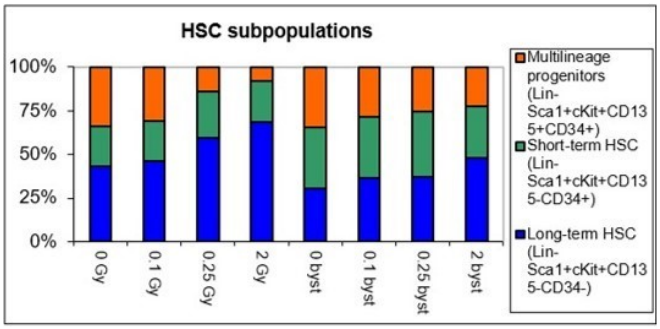
Soile Tapio

An interesting dose-dependent shift in the number of HSC subpopulations was seen in directly irradiated BM but also in the bystander BM: The proportion of long-term HSCs increased whilst the fraction of multilineage progenitors decreased (Figure 1).

In the spleen, the level of oxidative stress enzymes SOD2 and catalase was increased in irradiated and EV-treated animals. In addition, the level of the senescence marker p16INK4a was increased in both cases. These effects were observed only in the high-dose (2.0 Gy) group.

Regarding EV uptake by the unfractionated BM cell population, the irradiation of EVs at 2 Gy but not at 0.1 Gy reduced the uptake in non-irradiated cells. Similarly, the irradiated cells (2 Gy) were able to receive less EVs than the non-irradiated or low-dose (0.1 Gy) irradiated cells and if both EVs and cells were irradiated (2 Gy), the uptake was very low (9.5%) (Figure 2).

Photo: NNK

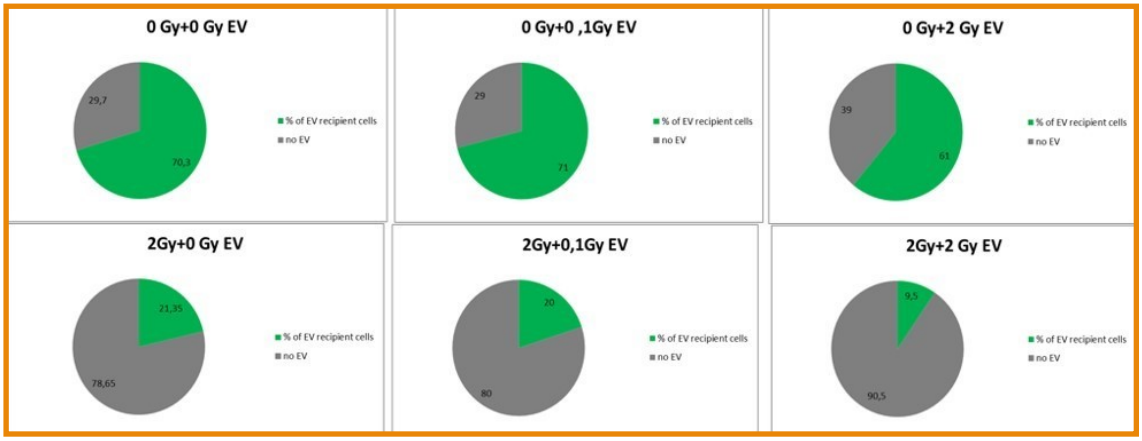


1) Changes in the fraction of haematopoietic stem cell subpopulations in directly irradiated and EV-treated mice.

Interestingly, EVs isolated from irradiated mice could in some BM subpopulations induce effects similar to those seen in irradiated animals. The number of haematopoietic stem cells (HSC) that were treated with EVs isolated 24 hours after irradiation was significantly reduced in the bystander animals in the short (24 hours) and long term (3 months). No effects were seen if the EVs were isolated 3 months after irradiation. Similar EV-mediated bystander effects were seen with lymphoid progenitor cells, myeloid progenitor cells, erythroid precursors, and mesenchymal stem cells, especially at the 2 Gy dose. The rate of apoptosis in HSCs increased strongly both in directly irradiated and EV-treated mice but only after high dose irradiation (2 Gy).

Taken together, firstly, our data show that bystander signals are transmitted by EVs inducing persistent changes in some but not all BM cell types. Secondly, BM-derived EV-mediated signals influence peripheral haematopoietic organs (spleen) by inducing protein expression changes (oxidative stress and senescence induction). Thirdly, the rate of EV uptake in BM is inhibited if the EVs originate from irradiated animals or if the BM has been irradiated before the EV introduction.

Photo: NNK



2) EV uptake by bone marrow cells.

Short and long-term effects of extracellular vesicles in radiation-induced bystander responses, Kis D., XXVII Annual Congress of the Hungarian Biophysical Society, Debrecen, Hungary, 26-29 August 2019, conference presentation

The effect of in vivo irradiation on the extracellular vesicle's cargo and uptake, Szatmári T., ISEV Annual Meeting, Kyoto, Japan, 25-29 April 2019, conference presentation

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German Research Center for Environmental Health

ID Card:

Keywords:
Mechanistic studies, EV function, EV uptake

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- GUF, Germany

Infrastructures:
Models and tools:
CBA/C57 Black murine models

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LEU-TRACK WP4

Identification of radiation-related and leukaemia-risk associated biomarkers in human leukaemia patients subjected to whole body irradiation

The objective of work package 4 is to characterize the phenotype and content of blood-derived extracellular vesicles (EVs) from leukaemia patients to identify leukaemia related and/or radiation exposure-related protein, miRNA or cell-surface markers and to compare them with markers identified in experimental animals.

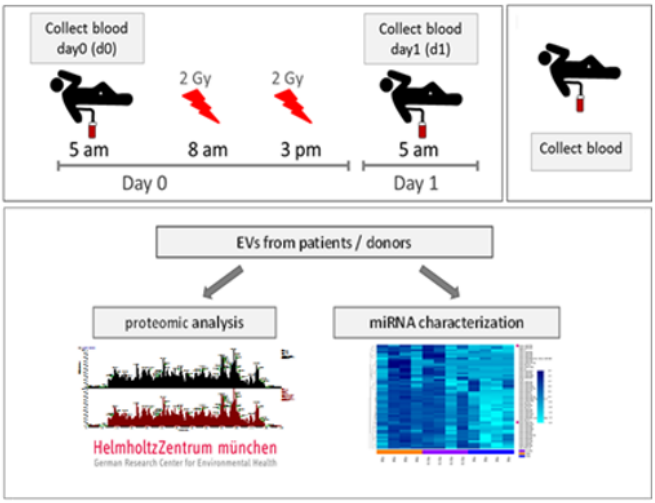

Photo: GUF

1) Workflow for identification of protein and miRNA cargo of EVs derived from leukaemic patients. EVs from leukaemic patients and healthy donors were isolated by ultracentrifugation and subjected to mass spectroscopy proteomic analysis and miRNA detection by Next Generation Sequencing (NGS, ongoing work).

Patients (n=11) with acute myeloid (AML) or acute lymphatic leukaemia (ALL) were conditioned for stem cell transplantation at the Department of Radiotherapy and Oncology, blood samples were collected before (d0) and after irradiation with 2 x 2 Gy (d1) using a linear accelerator, while age-and gender matched healthy volunteers (n=10) served as controls. In addition, CBA mice were irradiated with 0.1, 1, 3 Gy using image-guided radiotherapy performed with small animal radiation research platform (SARRP).

EVs were isolated by isolation kits or by ultracentrifugation (human samples) and were characterized for size and surface marker expression by flow cytometry and Western immunoblotting. These approaches indicate a size distribution of 500-900 nm, detection of typical EV markers such as CD9, CD81 and tumor susceptibility gene (TSG)101 expression in leukaemic patients and suitability of these particles for proteomic analyses that were performed at partner Helmholtz Center Munich (HMGU, Figure 1). By focusing on human samples, EVs were subjected to high-performance liquid chromatography coupled to mass spectrometry (LC-MSn) and six and 21 proteins were recognized upregulated or downregulated as compared to healthy donor controls. In principal component analysis (PCA, Figure 2), these deregulated proteins clustered around serum amyloids, alpha-acid glycoproteins, and plasma proteases. In addition, 14 proteins were found downregulated and 23 proteins were found upregulated in the EVs of patients after a 2 x 2 Gy whole body exposure.

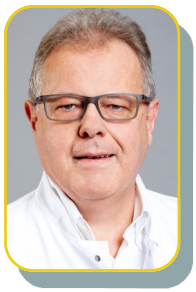

Photo: Goethe-University

Franz Rödel

In summary, our findings indicate that isolation protocol by ultracentrifugation for EVs from serum was successful. As compared to healthy controls and following irradiation, we have identified differentially regulated proteins in serum-derived EVs from leukaemic patients that may serve as possible biomarkers of leukaemogenesis and radiation exposure.

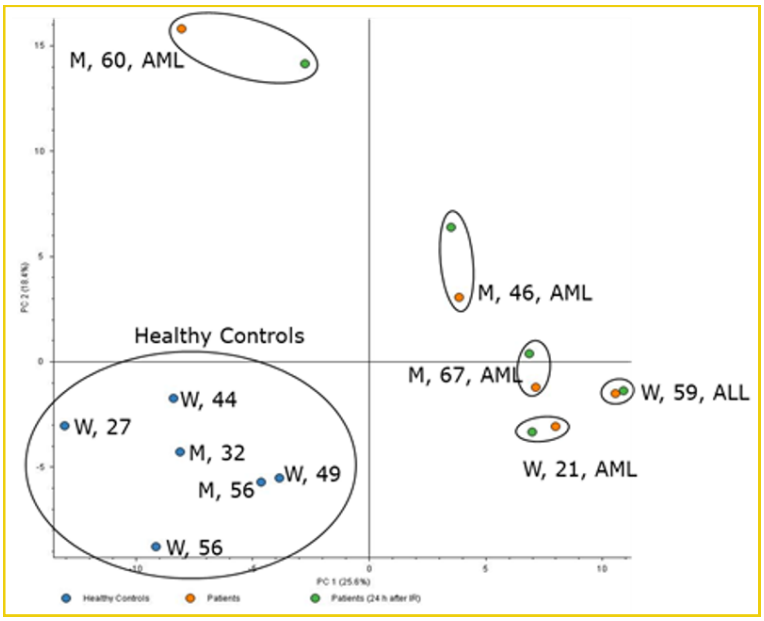

Photo: GUF, HMGU

2) Principal component analysis (PCA) based on all proteomic features of serum-derived EVs from healthy controls and leukaemic patients. Clustering of healthy control samples (blue) is observed. The sex (M/W), age, and the type of leukaemia if relevant is indicated. The PCA coordinates for the same patient before (orange) and after exposure to IR (green) were not markedly changed, indicating only small alterations in the EV cargo due to irradiation.

ID Card:

Keywords:
Leukaemia, extracellular vesicles, radiation-induced systemic effects, biomarkers

Work Package leader:
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Goethe-University Frankfurt am Main (GUF)

Partners:
- GUF, Germany
- HMGU, Germany
- NNK, Hungary
- PHE, United Kingdom

Infrastructures:
Cohorts:
Patients with AML, ALL
Analytical platforms:
CytoflexS flow cytometer, HELMHOLZ proteomic core facility

Contact:
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The Role of Extracellular Vesicles in Modulating the Risk of Low Dose Radiation-induced Leukaemia: Characterization of Vesicles by FACS, Eckert D. et al., DeGBS Annual Meeting, 23-25 September 2019, Mannheim, conference presentation

Characterization of serum-derived extracellular vesicles from leukaemic patients to identify leukaemic and radiation biomarkers, Eckert D. et al., DEGRO 2020, conference presentation

Special Issue 9
April 2020

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Access to INFRASTRUCTURES

Issue	Exposure platforms	Databases, Sample banks, Cohorts	Analytical platforms, Models & Tools
Published to date:			
Oct 2015, #1	FIGARO	FREDERICA	RENEB
Nov 2015, #2	B3, Animal Contamination Facility	The Wismut Cohort and Biobank	The Hungarian Genomics Research Network
Dec 2015, #3	Pulex Cosmic Silence	STORE	METABOHUB
Feb 2016, #4	SNAKE	French Haemangioma Cohort and Biobank	Dose Estimate, CABAS, NETA
Mar 2016, #5	Radon exposure chamber	3-Generations exposure study	PROFI
Apr 2016, #6	Biological Irradiation Facility	Wildlife TransferDatabase	Radiobiology and immunology platform (CTU-FBME)
May2016, #7	CIRIL	Portuguese Tinea Capitis Cohort	LDRadStatsNet
Jun 2016, #8	Mixed alpha and X-ray exposure facility	Elfe Cohort	ERICA Tool
Jul 2016, #9	SCRS-GIG	RES^{3}T	CROM-8
Sep 2016, #10	Facility radionuclides availability, transfer and migration	INWORKS cohort	France Génomique
Oct 2016 #11	LIBIS gamma low dose rate facility ISS	JANUS	Transcriptomics platform SCKCEN
Nov 2016, #12	Microtron laboratory	EPI-CT Scan cohort	CATI
Dec 2016, #13	Nanoparticle Inhalation Facility	UEF Biobanking	The Analytical Platform of the PREPARE project
Feb 2017, #14	Infrastructure for retrospective radon & thoron dosimetry	Chernobyl Tissue Bank	HZDR Radioanalytical Laboratories
Special Issue 1	1st CONCERT Call: CONFIDENCE, LDLensRad, TERRITORIES	1st CONCERT Call: CONFIDENCE, LDLensRad, TERRITORIES	1st CONCERT Call: CONFIDENCE, LDLensRad, TERRITORIES
Mar 2017, #15	Alpha Particles Irradiator Calibration Laboratory at KIT		SYMBIOSE
Apr 2017, #16	Changing Dose rate (SU) Low dose rate (SU)		Advanced Technologies Network Center
May 2017, #17	Chernobyl Exclusion Zone	Chernobyl clean-up workers from Latvia	BfS whole and partial body Counting
Jun 2017, #18	MELAF	Belgian Soil Collection	INFRAFONTIER
Jul 2017, #19	MICADO'LAB	Estchern Cohort	ECORITME
Sep 2017, #20	DOS NDS		CERES
Oct 2017, #21	CALLAB Radon Calibration Laboratory		CORIF
Nov 2017, #22	Calibration and Dosimetry Laboratory (INTE-UPC)	German airline crew cohort	Centre for Omic Sciences (COS)
Dec 2017, #23	NMG	Techa River Cohort (TRC)	iGE3
Special Issue 2	MEDIRAD	MEDIRAD	MEDIRAD
Feb 2018, #24	UNIPI-AmBe	Greek interventional cardiologists cohort	SNAP

Future events:

CONCERT Short Courses

20 April-1 May 2020

Assessment of long-term radiological risks from environmental releases, Technical University of Denmark, Risø Campus, Denmark

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Kasper Andersson

18-29 May 2020

Modelling radiation effects from initial physical events, University of Pavia, Italy

Contact:
Andrea Ottolenghi

To verify for possible modifications due to the COVID-19 outbreak!

See also on CONCERT website

Editorial Committee: Maria Panagiotopoulou, Jean-Michel Dolo, Laure Sabatier

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Access to INFRASTRUCTURES

Issue	Exposure platforms	Databases, Sample banks, Cohorts	Analytical platforms, Models & Tools
Published to date:			
Special Issue 3	2nd CONCERT Call: LEU-TRACK, PODIUM, SEPARATE, VERIDIC, ENGAGE, SHAMISEN-SINGS	2nd CONCERT Call: LEU-TRACK, PODIUM, SEPARATE, VERIDIC, ENGAGE, SHAMISEN-SINGS	2nd CONCERT Call: LEU-TRACK, PODIUM, SEPARATE, VERIDIC, ENGAGE, SHAMISEN-SINGS
Mar 2018, #25	IRRAD	MARiS	BIANCA
Apr 2018, #26	Forest observatory site in Yamakiya	BBM	OEDIPE
May 2018, #27	Belgian NORM Observatory Site	The German Thorotrast Cohort Study	VIB Proteomics Core
Jun 2018, #28	CERF	Mayak PA worker cohort	Geant4-DNA
Jul 2018, #29	TIFPA	RHRTR	D-DAT
Sep 2018, #30	HIT	The TRACY cohort	COOLER
Oct 2018, #31	PTB Microbeam	The BRIDE platform	BRENDA
Nov 2018, #32	AGOR Facility at KVI-CART LNK		MARS beamline at SOLEIL
Dec 2018, #33	PARISII	The ISIBELa cohort	CIEMAT WBC
Feb 2019, #34	The MIRCOM microbeam	The ISE cohort	EFFTRAN
Special Issue 4	NSRL	LSAH & LSDA	GeneLab
Mar 2019, #35	IRSE Experimental Farm	The MWF database	DSA Environmental Laboratory
Apr 2019, #36	PG stack at Barreiro, Portugal	CONSTANCES	The MCDA Tool
May 2019, #37	LERF	IMMO-LDRT01 cohort	Radiochemical and Radioactive Analysis Laboratory (INTE-UPC)
Jun 2019, #38	FAIR	The BACCARAT study	CIEMAT *In Vitro* Internal Dosimetry Laboratories
Jul 2019, #39	AMBIC	LSS	LRM
Sep 2019, #40	FRM II	REQUITE	TU Dublin Analytical Platform
Special Issue 5	CONFIDENCE	CONFIDENCE	CONFIDENCE
Special Issue 6	PODIUM	PODIUM	PODIUM
Special Issue 7	LDLensRad	LDLensRad	LDLensRad
Special Issue 8	ENGAGE	ENGAGE	ENGAGE
Special Issue 9	LEU-TRACK	LEU-TRACK	LEU-TRACK

Future events:

Other Events

19-24 April 2020
ICRER: 5th International Conference on Radioecology & Environmental Radioactivity, Amsterdam, The Netherlands

19-24 April 2020
IM2020: International Conference on Individual Monitoring, Budapest, Hungary

5-8 May 2020
1st ISORED scientific and organisation meeting, Sitges, Spain

27-29 May 2020
6th NERIS workshop: Operational and research achievements and needs to further strengthen preparedness in emergency management, recovery and response, Barcelona, Spain

28 September-2 October 2020
ERPW2020: European Radiation Protection Week 2020, Estoril, Portugal
Extended deadline for abstract submission:
30 April 2020

To verify for possible modifications due to the COVID-19 outbreak!

Editorial Committee: Maria Panagiotopoulou, Jean-Michel Dolo, Laure Sabatier