Ressortforschungsberichte zum Strahlenschutz

6th International Workshop on the Causes of Childhood Leukemia - Vorhaben 3619I02454

Auftragnehmer:
Valentum Kommunikation GmbH

Das Vorhaben wurde mit Mitteln des Bundesministeriums für Umwelt, Naturschutz und nukleare Sicherheit (BMU) und im Auftrag des Bundesamtes für Strahlenschutz (BfS) durchgeführt.

Bundesamt für Strahlenschutz

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Abschlussbericht

Vorhaben: 3619102454

6th International Workshop on the Causes of Childhood Leukemia

Auftragnehmer:
Valentum Kommunikation GmbH
Bischof-von-Henle Straße 2b
93051 Regensburg

Laufzeit des Vorhabens: Juli 2019 bis Februar 2020

Anlagen:
Veranstaltungsprogramm
Abstractband

1. Zielsetzung

Beobachtungen aus epidemiologischen Studien weisen auf einen möglichen Zusammenhang zwischen niederfrequenten Magnetfeldern und einem erhöhten Risiko für Leukämie im Kindesalter hin. Auch gibt es Beobachtungen, dass niedrige Dosen ionisierender Strahlung mit einem erhöhten Auftreten von Leukämie in Kindern einhergehen. Für beide Beobachtungen sind bisher keine zufriedenstellenden, wissenschaftlich fundierten Erklärungen gefunden worden.
Dies veranlasste das Bundesamt für Strahlenschutz (BfS), die Forschung zu Leukämie im Kindesalter zu intensivieren und den möglichen Ursachen und Zusammenhängen in internationalen Workshops nachzugehen.
Im Rahmen des 6. Internationalen Workshops wurde der aktuelle Forschungsstand mit internationalen Experten in einer dreitägigen Veranstaltung umfassend beleuchtet, um sich der Thematik aus unterschiedlichen wissenschaftlichen Perspektiven zu nähern, Wissenslücken zu identifizieren und, wo nötig, neue Forschung zu initiieren

1.1 Einzelzielsetzung

Unmittelbares Ziel der Veranstaltung war es, einen Überblick über den aktuellen Forschungsstand aus der Perspektive verschiedener wissenschaftlicher Disziplinen zu erhalten und offene Fragen zu identifizieren, auf deren Grundlage die Forschung fortgeführt werden sollte. Hierfür wurden internationale Referentinnen und Referenten, die als Experten auf ihrem jeweiligen Fachgebiet gelten, nach Freising eingeladen, um sich der Thematik möglicher Gründe für Leukämie im Kindesalter anzunähern. Erweitert wurde der Teilnehmerkreis durch weitere Expertinnen und Experten, die den Workshop als Teilnehmende mit ihrem Fachwissen ergänzten.

Der Workshop wurde in fünf inhaltlich aufeinander abgestimmte Sessions eingeteilt und durch zwei spezielle Sitzungen ergänzt.

Die inhaltlichen Details und Vorbereitungen des Workshops wurden vom Bundesamt für Strahlenschutz erarbeitet. Die organisatorische Umsetzung erfolgte mit Unterstützung eines externen Dienstleisters (Valentum Kommunikation GmbH).

1.2 Voraussetzungen für den Workshop

Der Workshop fand im Tagungssaal des Viva Vita in Freising statt. Der Veranstaltungsort ist vom Flughafen München mit einer direkten Regionalbahn- oder Busverbindung in ca. 30 Minuten zu erreichen. Das Tagungscatering wurde durch den Veranstaltungsort geleistet.

1.3 Planung und Ablauf des Workshops

Die Aufgaben für die Organisation des Workshops wurden in drei Arbeitspakete eingeteilt.

AP 1: Planung des Workshops:

- Auswahl eines Veranstaltungsortes und des Termins
- Management der Einladungen und Ankündigungen, Organisation der Pausenversorgung
- Einrichtung der notwendigen technischen Infrastruktur
- Einrichtung und Führung eines Tagungsbüros
- Reisemanagement der Teilnehmenden
- Organisation eines gemeinsamen Conference Dinners
- Einladungsversand

AP 2: Durchführung des Workshops

- Unterstützung bei der Einhaltung des Programmablaufs (siehe Anhang)
- Koordination der Dienstleister vor Ort (Technik, Catering, Conference Dinner)
- Betreuung der Rednerinnen und Redner sowie Gäste vor Ort (Reisemanagement, Registrierung, Beantwortung von organisatorischen Rückfragen)

AP 3: Nachbereitung

- Fotodokumentation
- Reisekostenabrechnung
- Abschlussbericht

1.4 Organisatoren

Die dreitägige Veranstaltung „6th International Workshop on the Causes of Childhood Leukemia“ wurde vom Bundesamt für Strahlenschutz durchgeführt.

Die Organisation und praktische Durchführung wurde durch die Agentur Valentum Kommunikation GmbH (Bischof-von-Henle Straße 2b | 93051 Regensburg) unterstützt.

2. Durchführung des Workshops

2.1 Hintergrund

Alleiniger Veranstalter des Workshops, der vom 20. bis 22. November 2019 in Freising stattfand, war das Bundesamt für Strahlenschutz im Auftrag des Bundesministeriums für Umwelt, Naturschutz und nukleare Sicherheit. Unmittelbar nach dem Auftaktgespräch am 3. Juli 2019 wurde die Veranstaltungswebseite www.leukemia-workshop.de/ eingerichtet. Hier wurden laufend aktuelle Informationen zum Programm und dem Ablauf der Tagung sowie die Möglichkeit zur Registrierung bereitgestellt.

2.2 Programm

Mit 22 Vorträgen von geladenen Rednerinnen und Rednern aus zehn Ländern wurde das Programm des dreitägigen Workshops gestaltet. Dies umfasste neben den vom Bundesamt für Strahlenschutz eingeladenen Referenten auch Redner, deren Organisation und Koordinierung im Rahmen von zwei Special Sessions durch Ximena Vergara und Ben Spycher erfolgte. Zusätzlich ergänzten vier Kurzvorträge sowie vier Poster von teilnehmenden Gästen das Programm.

Folgende Punkte sollten im Rahmen der Veranstaltungen erarbeitet werden und dienten als Grundlage der Diskussionen:

- Ionisierende und nichtionisierende Strahlung als Risikofaktoren für Leukämie im Kindesalter
- Mechanismen der Leukämieentwicklung, einschließlich genetischer und epigenetischer Faktoren, der Rolle des Immunsystems und Umweltrisikofaktoren
- Hintergrundstrahlung und das Risiko einer Leukämie
- Tiermodelle zur Untersuchung von Leukämie

Zwischen den Programmpunkten konnte das Publikum Fragen zu den Präsentationen stellen und Probleme oder Streitpunkte diskutieren. Teilnehmende, Rednerinnen und Redner und Veranstalter tauschten sich hier über das Gehörte aus und erörterten gemeinsam Ansatzpunkte für die Weiterentwicklung der Forschung. Auf Basis des erhaltenen Feedbacks wird nun die weitere Vorgehensweise erarbeitet.

In den Programmpausen sowie bei einem gemeinsamen Conference Dinner am Abend des zweiten Veranstaltungstages konnten die Gäste den Austausch sowie das Networking im lockeren Rahmen fortsetzen.

Insgesamt nahmen 66 Personen aus 13 Ländern am Workshop teil. Die Teilnahmegebühr betrug 200 Euro, zuzüglich 50 Euro für eine Teilnahme am Conference Dinner.

2.3 Beteiligte Akteure des Workshops

Geladene Rednerinnen und Rednern

- Borkhardt, Arndt | Universitätsklinikum Düsseldorf, Germany
- Cazzaniga, Giovanni | Clinica Pediatrica Università di Milano Bicocca, Italy
- Dwyer, Terence | University of Oxford, United Kingdom
- Erdmann, Friederike | Danish Cancer Society Research Center, Denmark
- Feychting, Maria | Institute of Environmental Medicine, Sweden
- Fischer, Ute | Universitätsklinikum Düsseldorf, Germany
- Goujon, Stefanie | Epidemiology and Biostatistics Sorbonne Paris Cité Research Center (CRESS), Inserm, France
- Hauer, Julia | Universitätsklinikum Dresden, Germany
- He, Jianrong | University of Oxford, United Kingdom
- Kendall, Gerald | University of Oxford, United Kingdom
- McKay, Jill | Northumbria University, United Kingdom
- Menéndez, Pablo | University of Barcelona, Spain
- Sánchez-García, Isidro | Instituto de Biologia Molecular y Celular del Cancer (IBMCC) of the Spanish National Research Council (CSIC), Spain
- Schüz, Joachim | International Agency for Research on Cancer (IARC/WHO), Section of Environment and Radiation, France
- Spycher, Ben | Institute of Social and Preventive Medicine, University of Bern, Switzerland

Special Session: Animal Models

- Broccardo, Cyril | Institut National de la Santé et de la Recherche Médicale (INSERM), University Toulouse, France
- Cobaleda, César | Spanish Research Council (CSIC) at the Centro de Biología Molecular Severo Ochoa, Spain
- Kogan, Scott | Department of Laboratory Medicine & Helen Diller Family Comprehensive Cancer Center, University of California, USA
- Izraeli, Shai | Division of Pediatric Hematology and Oncology, Schneider Children's Medical Center of Israel, Israel
- Vergara, Ximena | Electric Power Research Institute, USA

Special Session: Background Radiation

- Kreis, Christian | Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland
- Mazzei, Antonella | Institute of Social and Preventive Medicine, University of Bern, Switzerland

3. Ergebnisse

Für einen Überblick über den während des Workshops präsentierten Forschungsstand sind im Anhang die eingereichten Abstracts beigefügt.

Kosten- und Zeitplanung wurden eingehalten.

Veranstaltungsprogramm

Wednesday, November 20th

From 11.00 am	Registration | Welcome coffee
	Special Session: Animal Models *Chair: Ximena Vergara*
12.00 - 12.30 am	Introductions & Purpose: Why are we here? *Ximena Vergara*
12.30 - 1.00 pm	Childhood acute lymphoblastic leukemia - An overview and the challenges of modeling using human progenitors *Shai Izraeli*
1.00 - 1.30 pm	Stem-cell based animal model of Childhood pB-ALL *César Cobaleda*
1.30 - 2.00 pm	Cdkn2a deficient & Cdkn2a deficient/ETV6-RUNX1 mouse models of lymphoblastic leukemia *Scott Kogan*
2.00 - 2.30 pm	PAX5-ELN oncoprotein promotes multistep B-cell acute lymphoblastic leukemia in mice *Cyril Broccardo*
2.30 - 3.30 pm	Discussion - Speaker Panel *Moderated by Ximena Vergara, Shai Izraeli and Kerry Broom*
3.30 - 4.00 pm	**Coffee break**
	Session 1: Opening and Introduction *Chair: Federal Office for Radiation Protection*
4.00 - 4.15 pm	Welcome, short history and scope of the workshop *Gunde Ziegelberger, Federal Office for Radiation Protection*
4.15 - 4.30 pm	Federal Office for Radiation Protection activities: Summary of pilot projects *Sabine Hornhardt, Federal Office for Radiation Protection*
4.30 - 5.15 pm	Magnetic fields and childhood leukemia *Maria Feychting*
5.15 - 6.00 pm	Review of ionizing radiation and childhood leukemia *Ben Spycher*
From 7.00 pm	Informal Get-together | Weißbräu Huber | General-von-Nagel-Straße 5, 85354 Freising

Thursday, November 21st

From 8.30 am	Registration | Welcome coffee
	Session 2: Genetic and epigenetic factors *Chair: Federal Office for Radiation Protection*
9.00 - 9.30 am	Infections-driven B-precursor leukaemias are mediated by Activation Induced Deaminase (AID)-independent mechanisms *Arndt Borkhardt*
9.30 - 10.00 am	Pre-leukemic clones in healthy newborns *Ute Fischer*
10.00 - 10.30 am	Host genomics in acute leukemia of childhood *Julia Hauer*

10.30 - 11.00 am	**Coffee break**
11.00 - 11.30 am	Cell-of-origin and immunotherapeutic targets for MLLr B-ALL *Pablo Menéndez*
11.30 - 12.00 am	Environmental Exposures and Childhood Leukemia - DNA methylation as a Mediating Mechanism *Jill McKay*
12.00 - 12.30 am	The Making of Leukemia: Epigenetic Priming in Leukemia Initiation *Isidro Sánchez-García*
	Short Talk
12.30 - 12.45 am	A rare RAD21 mutation in a family with history of cancer *Franziska Auer*
12.45 - 1.45 pm	**Lunch break**
	Session 3: Role of the immune system *Chair: Federal Office for Radiation Protection*
1.45 - 2.15 pm	Maternal infections during pregnancy and childhood leukaemia: A systematic review of previous evidence and a pooled analysis from six international birth cohorts *Jianrong He*
2.15 - 2.45 pm	Inflammation favors ETV6-RUNX1 positive pre-leukemia in a model of bone marrow niche *Giovanni Cazzaniga*
2.45 - 3.15 pm	B-cell identity as a metabolic barrier against malignant transformation *Lai N. Chan [Cancelled]*
3.15 - 3.45 pm	**Coffee break**
	Short talks *Chair: Federal Office for Radiation Protection*
3.45 – 4.00 pm	Commensal gut microbiota protects from infection driven acute lymphoblastic leukemia *Carolina Vicente-Dueñas*
4.00 – 4.15 pm	The role of extracellular vesicles in ionizing radiation induced bone marrow pathologies *Katalin Lumniczky*
4.15 – 4.30 pm	Ionizing radiation induces AML related changes in the cargo of extracellular vesicles from haematopoetic system *Tünde Szatmári*
4.30 – 5.00 pm	**Poster Session**
	TCF3-PBX1 can arise prenatally *Daniel Hein*
	Early initiating events in childhood leukaemia: Exploring the role of DNA methylation & Does Benzene Exposure Influence Chromosomal Translocation Events Involved in Childhood Leukaemia? *Jill McKay*
	Childhood Leukemia - Influence of Extremely Low Frequency Magnetic Fields on the Development of the Disease *Dmitrij Sachno*
From 7.00 pm	Conference Dinner | Bräustüberl | Weihenstephaner Berg 10, 85354 Freising

Friday, November 22nd

From 8.30 am	Registration | Welcome coffee
	Session 4: Environmental risk factors *Chair: Federal Office for Radiation Protection*
9.00 - 9.30 am	New Results from the Childhood Leukemia International Consortium (CLIC) *Joachim Schüz*
9.30 - 10.00 am	Current research and future opportunities in the International Childhood Cancer Cohort Consortium *Terence Dwyer*
10.00 - 10.30 am	Space-time Clustering of Childhood Leukaemia: A Systematic Review and Pooled Analysis *Christian Kreis*
10.30 - 11.00 am	**Coffee break**
	Special Session: Background radiation *Chair: Ben Spycher*
11.00 – 11.20 am	An update on the study of childhood cancer and natural radiation in Great Britain *Gerald Kendall*
11.20 – 11.40 am	Ecological association between residential natural background radiation exposure and the incidence rate of childhood central nervous system tumors in France, 2000–2012 *Stéphanie Goujon*
11.40 – 12.00 am	Background Ionizing Radiation and the Risk of Childhood Cancer: A Census-Based Nationwide Cohort Study - New Results from Switzerland *Antonella Mazzei*
12.00 - 1.00 pm	**Small Lunch**
	Session 5: Looking around and forward – what to do next? *Chair: Federal Office for Radiation Protection*
1.00 - 1.30 pm	Variations and trends in incidence of lymphoid leukaemia in children: Results from 131 population-based cancer registries around the globe *Friederike Erdmann*
1.30 - 2.30 pm	Summing up/Discussion *Federal Office for Radiation Protection & Joachim Schüz*

Bundesamt für Strahlenschutz

6th International Workshop on the Causes of Childhood Leukemia

20th – 22nd November 2019 | Freising

Special Session: Animal Models

Childhood acute lymphoblastic leukemia - an overview and the challenges of modeling using human progenitors

Shai Izraeli | Division of Pediatric Hematology and Oncology, Schneider Children's Medical Center of Israel, Israel

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Bundesamt für Strahlenschutz

Special Session: Animal Models

Stem-cell based animal model of Childhood pB-ALL

César Cobaleda | Spanish Research Council (CSIC) at the Centro de Biología Molecular Severo Ochoa, Spain

Exposure to extremely low-frequency magnetic fields (ELF-MFs) has been classified by the International Agency for Research on Cancer (IARC) as "possibly carcinogenic to humans," based on limited scientific evidence concerning childhood leukemia. This assessment emphasized the lack of appropriate animal models recapitulating the natural history of this disease. Childhood B-cell acute lymphoblastic leukemia (B-ALL) is the result of complex interactions between genetic susceptibility and exposure to exogenous agents. The most common chromosomal alteration is the ETV6-RUNX1 fusion gene, which confers a low risk of developing the malignancy by originating a preleukemic clone requiring secondary hits for full blown disease to appear. To develop potential prophylactic interventions, we need to identify the environmental triggers of the second hit. Recently, we generated a pB-ALL mouse model of the human ETV6-RUNX1+ preleukemic state. In the ARIMMORA pilot study, we exposed 34 Sca1-ETV6-RUNX1 mice (vs. 27 unexposed) to a 50Hz magnetic field of 1.5mT with both fundamental and harmonic content, with an on/off cycle of 10min/5min, for 20 h/day, from conception until 3 months of age. Mice were monitored until 2 years of age and peripheral blood was periodically analyzed by flow cytometry. One of the exposed mice developed pB-ALL while none of the non-exposed did. Although the results are statistically non-significant due to the limited number of mice used in this pilot experiment, overall, the results show that the newly developed Sca1-ETV6-RUNX1 mouse can be successfully used for ELF-MF exposure studies about the etiology of childhood pB-ALL.

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Bundesamt für Strahlenschutz

Special Session: Animal Models

Cdkn2a deficient & Cdkn2a deficient/ETV6-RUNX1 mouse models of lymphoblastic leukemia

Scott Kogan | Department of Laboratory Medicine & Helen Diller Family Comprehensive Cancer Center, University of California, USA

Our research group has worked to understand mechanisms by which lymphoblastic leukemia develops. Given the high frequency of B lymphoblastic leukemia/lymphoma with t(12;21)ETV6-RUNX1 in human children, we set out to develop a mouse model of this leukemia that would be amenable to mechanistic studies. We found that mice carrying a single copy inducible ETV6-RUNX1 transgene demonstrated variegated hematopoietic expression of this transgene when induced with a Tek2-Cre allele. Our results with these animals paralleled prior and subsequent experience with expression of ETV6-RUNX1 in mouse blood cells: in a specific pathogen free environment, in the absence of additional genetic lesions or mutagenesis, the mice did not develop more disease or different disease from that observed in control animals. Nonetheless, the variegated nature of gene expression in the model demonstrated that although ETV6-RUNX1 is viewed as a B-cell lymphoblastic leukemia oncogene, it can in fact impair B-cell development. Additional work with this model showed that radiation mutagenesis could initiate T-cell and myeloid leukemias in these mice. Given the association of ETV6-RUNX1 with B-cell leukemia, we crossed the transgene into mice already predisposed to B-cell leukemia/lymphoma: Cdkn2a deficient animals. (Of note, ~1/4 of human children with B-lymphoblastic leukemia with ETV6-RUNX1 fusions also have deletions of CDKN2A.) In the mouse FVB/N strain, in which most of our experiments have been performed, about 25% of Cdkn2a null mice develop B-cell leukemia/lymphoma, many with lymphoblastic character. The addition of the ETV6-RUNX1 transgene accelerated disease development and increased B-cell leukemia/lymphoma penetrance to about 50% of Cdkn2a hull animals. We have used the Cdkn2a deficient & Cdkn2a deficient/ETV6-RUNX1 mouse models of leukemia/lymphoma to study interactions of genetics, toxins, the immune system, and the microbiome on the development of leukemia/lymphoma. Results of our ongoing studies will be presented and discussed.

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Bundesamt für Strahlenschutz

Special Session: Animal Models

PAX5-ELN oncoprotein promotes multistep B-cell acute lymphoblastic leukemia in mice

Cyril Broccardo | Institut National de la Santé et de la Recherche Médicale (INSERM), University Toulouse, France

Laura Jamrog[a,1], Guillaume Chemin[b,1], Vincent Fregona[a], Lucie Coster[c], Marlène Pasquet[d], Chloé Oudinet[b], Nelly Rouquié[a], Naïs Prade[a,c], Stéphanie Lagarde[a,c], Charlotte Cresson[a], Sylvie Hébrard[e], Ngoc Sa Nguyen Huu[b], Marina Bousquet[e], Cathy Quelen[e], Pierre Brousset[e], Stéphane J. C. Mancini[f], Eric Delabesse[a,c], Ahmed Amine Khamlichi[b,2], Bastien Gerby[a,2], and Cyril Broccardo[a,2]

PAX5, a gene encoding a key transcription factor in B cell differentiation, is altered in one third of B-cell acute lymphoblastic leukaemia (B-ALL). Its structural alterations (point mutations and translocations) are considered as primary oncogenic events of B-ALL while its deletion can be considered as an additional hit in the leukaemia process. Despite the well-known role of PAX5 as haploinsufficient tumour suppressor gene in human B-ALL, the function of PAX5 fusion proteins in B-ALL initiation and transformation is less defined. Our previous work reported a new chromosomal t(7;9)(q11;p13) translocation in human B-ALL that juxtaposes PAX5 and the sequence of elastin ELN (Bousquet et al., Blood 2007). To study the function of the resulting PAX5-ELN fusion protein in B-ALL development, we generated a transgenic mouse model in which PAX5-ELN is expressed from the IgH locus to ensure its early and restricted expression in B cell compartment. PAX5-ELN transgenic mice efficiently developed B-ALL with an incidence of 80%. Leukemic transformation systematically occurs with a minimal latency of 3 months suggesting requirement of additional oncogenic events. Exome sequencing revealed that mouse B-ALL induced by PAX5-ELN is associated with recurrent secondary mutations on PTPN11, KRAS, PAX5 and JAK3 genes affecting key signaling pathways required for cell proliferation. At the pre-leukemic stage, PAX5-ELN induces a partial blockade of B-cell differentiation in vivo characterized by an aberrant expansion of the pro-B cell compartment in steady state and in transplantation assay. Finally, our molecular and computational approaches identified PAX5-ELN-regulated gene candidates that establish the molecular bases of the preleukemic state to drive B-ALL initiation. Hence, our study provides a new in vivo model recapitulating the multistep leukemogenesis process of human B-ALL and strongly implicates PAX5 fusion proteins as potent oncoproteins in leukemic development (Jamrog et al., PNAS, 2018).

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Session 1: Opening and Introduction

Magnetic fields and childhood leukemia

Maria Feychting | Institute of Environmental Medicine, Karolinska Institute, Sweden

Exposure to extremely low frequency magnetic fields (ELF-MF) as a potential risk factor for childhood leukemia has been studied since the late 1970s, and there are currently around 40 epidemiological studies available. These are of varying design and quality and have used different exposure assessment methods. Exposures levels potentially associated with increased risk are rare in the general population, and so is the disease. Thus, most studies have had limited statistical power, which has affected choice of exposure categorizations and analytical strategies. The most informative evidence comes from the pooling of original data from multiple studies, allowing harmonized exposure indices and more reliable analyses of higher exposure levels. There are currently four pooled analyses of ELF-MF exposure available; two that included data until the year 2000, with different inclusion criteria but largely overlapping; the third covering studies published after the first two pooling projects, and a fourth study pooling results on nighttime exposure. In addition, a few new studies have been published during later years, which have not yet been included in any pooled analysis. All four pooled analyses reported a modestly raised risk estimate (1.5 – 2-fold) for childhood leukemia among children exposed to residential magnetic field levels ≥0.3 μT or ≥0.4 μT, and there was no difference between nighttime exposure and assessment over 24 h. Findings from the most recent pooled analysis were weaker, and the newer studies have generally not confirmed the findings of a raised risk, but these studies have considerable statistical uncertainty. Overall, the hypothesis that ELF-MF increases the risk of childhood leukemia is still supported by the available epidemiological evidence, although it has become somewhat weaker.

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Bundesamt für Strahlenschutz

Session 1: Opening and Introduction

Review of ionizing radiation and childhood leukaemia

Ben Spycher | Institute of Social and Preventive Medicine, University of Bern, Switzerland

It is well established that moderate to high doses of ionizing radiation increase the subsequent risk of leukaemia. The evidence for this comes from studies of Japanese atomic bomb survivors (Life Span Study, LSS) and populations exposed to therapeutic radiation. The highest relative increases in leukaemia risks have been shown to occur after exposure during childhood. In my presentation, I will focus on the effects on leukaemia risks following low dose exposure (<100 mSv) for which the evidence is less established. Models derived from the LSS predict that the excess relative risk (EER) begins to increase rapidly about two years after exposure in childhood rising to approximately 50 Gy-1 some 7 years after exposure. Assuming a linear dose-response relationship with no threshold below which there are no effects on leukaemia risks, this would suggest that a considerable proportion of childhood leukaemia in the general population may be induced by common sources of radiation including background radiation or diagnostic radiology. Indeed, estimates for the UK and France suggest that up to 20% of childhood leukaemia cases may be attributable to background ionizing radiation.

The strongest evidence for leukaemia risks associated with exposure to low doses (<100 mSv) of ionizing radiation during childhood comes from a recent pooled analysis of 9 cohort studies including the LSS and medically exposed groups. The estimated relative risks were 2.56 (95 % CI: 1.09, 5.06; p-trend=0.03) for acute myeloid leukaemia and 5.66 (95% CI: 1.35, 19.71; p-trend=0.02) for acute lymphoblastic leukaemia.

Several nationwide record-based studies in European countries have investigated the possible association of natural background radiation and childhood cancers. The first of these studies, which was carried out in Denmark, found an increased risk of leukaemia in people exposed to high levels of residential radon. Later, a larger UK study found that the risk of childhood leukaemia increased by 12% (95% CI: 3-22%) per mSv cumulative equivalent dose to the red bone marrow from terrestrial gamma radiation, but no evidence of an association for residential radon. Similarly, a census-based cohort study from Switzerland found no evidence of associations between childhood cancers and radon, but evidence of associations for leukaemia and brain tumours with total radiation dose from terrestrial gamma and cosmic radiation. For both these diagnostic groups a risk increases of 4% (95% CI: 0-8%) per mSv cumulative effective dose to the whole body was estimated. Despite large uncertainties, the risk estimates from the UK and Swiss studies for childhood leukaemia in relation to gamma radiation are in broad agreement with those from the LSS. In contrast, a more recent large record-based case-control study from France found no evidence for an association between childhood leukaemia and background radiation, neither for radon nor for terrestrial gamma radiation. A record-based case-control study in Finland reported weak evidence for increased risks of childhood leukaemia with exposure to terrestrial gamma radiation, but only in young children aged 2-6 years (corresponding to the period of peak incidence). A recent German ecologic study did not find evidence of an association between childhood leukaemia and ambient gamma dose rates but did find an association for brain tumors.

I will discuss the discrepancies between studies on childhood leukaemia and background radiation in view of their methodological limitations and propose ways forward in this area of research.

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Session 2: Genetic and epigenetic factors

Infections-driven B-precursor leukaemias are mediated by Activation Induced Deaminase (AID)-independent mechanisms

Arndt Borkhardt | Düsseldorf University Hospital, Germany

Arndt Borkhardt, Guillermo Rodríguez-Hernández, Friederike V. Opitz, Carolina Vicente-Dueñas, Julia Hauer, Almudena R. Ramiro, Isidro Sánchez-García

The prerequisite to develop preventive strategies in childhood B-cell precursor acute lymphoblastic leukemia (B-ALL) is to decipher its etiology. The current working model suggests that infection or chronic inflammation triggers B-ALL development through induction of activation-induced cytidine deaminase (AID; also known as AICDA) expression in precursor B cells. Evidence supporting this view has been largely acquired through the use of ex vivo functional studies involving bone marrow transplantation. However, whether this mechanism also governs native non-transplant B-ALL development is entirely unclear. We examined here whether AID is required in the aetiology of B-ALL for clonal evolution of pre-malignant precursor B-cells using two in vivo genetic approaches. In a loss-of-function experiment, we tested the role of AID as a driver of leukaemogenesis in Pax5-haploinsufficient mice that are prone to B-ALL upon natural exposure to infectious pathogens. Surprisingly, genetic deletion of AID did not affect the latency and penetrance of B-ALL, suggesting that AID was dispensable for clonal evolution in the Pax5-haploinsufficient mice. In a gain of function experiment, we next tested the effect of premature expression of AID from earliest pro-B-cell stages in B-cell transformation. The generation of AID off-target mutagenic activity in precursor B-cells did not promote B-ALL development. Likewise, known drivers of human B-ALL were not preferentially targeted by AID. Overall, these results suggest that infectious stimuli can promote malignant B-cell leukaemogenesis through AID-independent mechanisms and might have profound impact to finger approaches for preventing infection-driven B-ALL.

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Session 2: Genetic and epigenetic factors

Pre-leukemic clones in healthy newborns

Ute Fischer | Düsseldorf University Hospital, Germany

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Pediatric B cell acute lymphoblastic leukemia (ALL) is characterized by recurrent primary numerical or structural alterations. The most common alteration is the chromosomal translocation t(12;21). The translocation generates the ETV6-RUNX1 (synonymous to TEL-AML1) fusion gene and provides a specific molecular marker of the malignant clone. Retrospective analyses of archived neonatal blood spots, molecular screening of cord blood and studies of monozygotic twins concordant for leukemia employing this marker have demonstrated that the ETV6-RUNX1+ and other subtypes of B ALL frequently emerge before birth during fetal hematopoiesis. The ETV6-RUNX1 translocation is only mildly oncogenic and secondary mutations are clearly required for final leukemia onset.

Several studies have analyzed the incidence of the ETV6-RUNX1+ pre-leukemic cell clones in newborns using RNA derived from cord blood or peripheral blood as a specimen. The suggested incidence ranged from 0.01% (equaling the corresponding leukemia rate) to ↓8% (exceeding the leukemia incidence by a factor of 800). The discrepancies were likely due to drawbacks associated with RNA-based PCR techniques: the possible generation of (1) false-positive results caused by contamination and (2) false-negative results caused by RNA instability, low expression of the ETV6-RUNX1 transcript and low numbers of pre-leukemic cells amongst a majority of normal cells.

Funded by the Federal Office for Radiation Protection (BfS)/the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) we therefore developed a novel, highly specific and sensitive DNA-based technique termed GIPFEL (for „Genomic Inverse PCR for Exploration of Ligated Breakpoints“) to detect translocations without prior knowledge of the exact breakpoint. We applied this technique in a population-based retrospective screening to 1,000 umbilical cord blood samples. These studies demonstrated that pre-leukemic cell clones carrying the ETV6-RUNX1 translocation at levels detectable by GIPFEL (at least 1 pre-leukemic cell among 10,000 cells) are present in ↓5% of healthy newborns. The translocation is therefore 500-fold more frequent than the corresponding leukemia incidence (1/10,000). Thus, translocation-carrying clones are likely present in a high number of healthy individuals who will never develop leukemia. Our results therefore strengthen the importance of environmentally or spontaneously caused secondary oncogenic events in the development of ETV6-RUNX1+ ALL. Further studies correlating epidemiological and experimental data are clearly necessary to understand the pathogenesis of childhood leukemia.

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Session 2: Genetic and epigenetic factors

Host genomics in acute leukemia of childhood

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The contribution of somatic variants in the development, progression and therapy response of acute lymphoblastic leukemia is well known. Constitutional genetic variance are estimated to be present in up to 4-5% of leukemia patients. However, reports of novel predisposition syndrome are steadily increasing.

Classical genetic predisposition to ALL relates to genetic variants in hematopoietic transcription factors such as Pax5, IKZF1, ETV6 and others. Recently ALL has been described in connection with syndromic disease such as Cornelia-de-Lange and Rubinstein-Taybi syndrome thus suggesting a connection between variants in cohesin complex genes and CRBBP/EP300 pathway respectively.

Common to all genetic predisposition syndromes is reduced penetrance, thus environmental factors such as infection, irradiation, lifestyle habits contribute to final leukemia development.

Clinically the most relevant aspect is to take advantage of the knowledge about genetic predisposition in affected children and to come up with personalized therapy adaption or surveillance recommendation. Therefore, we propose genetic screening for predisposition in every newly diagnosed child and their parents. Combination of the genetic fingerprint with drug sensitivity data will be a reasonable measure to predict therapy related toxicity and come up with individual therapy adaption.

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Session 3: Genetic and epigenetic factors

Mutations in monozygotic twins

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Session 2: Genetic and epigenetic factors

Environmental Exposures and Childhood Leukemia - DNA methylation as a Mediating Mechanism

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The aetiology of childhood acute lymphoblastic leukaemia (ALL) is unclear. Whilst it is widely accepted that genetic abnormalities are initiating events in ALL development, it has been established that these alone are not sufficient for leukaemic transformation. Epidemiological evidence suggests various in utero and post-natal environmental exposures may alter risk of childhood ALL including parental smoking, maternal folate intake, maternal caffeine intake, air pollution, paints, solvents and pesticides, day-care attendance and infection. However, as ALL is relatively rare and exposure data is often collected retrospectively, the strength of evidence for these associations can be limited. Additionally, there is little current understanding of how these environmental factors may mechanistically influence ALL development.

DNA methylation is one mechanism by which genes are regulated, with aberrant methylation leading to gene dysregulation. Aberrant methylation is reported in ALL and may be an important contributor to childhood ALL aetiology. Importantly, DNA methylation patterns can be influenced by environmental exposures, suggesting a potential mediating mechanism between environment and ALL disease risk.

To investigate this, we have used novel 'Meet in the Middle' and Mendelian Randomisation approaches to examine the potential role of DNA methylation as a mediating mechanism between environmental exposures and ALL. Together our data suggests that DNA methylation may indeed play such a role. These studies may provide better understanding of the early events in the development of childhood leukaemia and strengthen the evidence for a role of environmental factors in the causes of ALL. Further understanding of the role of DNA methylation and potentially modifiable risk factors in childhood leukaemia aetiology may aid the development of preventative interventions as well as provide biomarkers for disease screening.

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Session 2: Genetic and epigenetic factors

The Making of Leukemia: Epigenetic Priming in Leukemia Initiation

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Due to the clonal nature of human leukemia evolution, all leukemic cells carry the same leukemia-initiating genetic lesions, independently of the intrinsic tumoral cellular heterogeneity. However, the latest findings have shown that the mode of action of oncogenes is not homogeneous throughout the developmental history of leukemia. Studies on different types of hematopoietic tumors have shown that the contribution of oncogenes to leukemia is mainly mediated through the epigenetic priming of the leukemia-initiating target cell. This driving of cancer by a malignant epigenetic stem cell rewiring is, however, not exclusive of the hematopoietic system, but rather represents a common tumoral mechanism that is also at work in epithelial tumors. Tumoral epigenetic priming is therefore a new type of interaction between genes and their target cells, in which the action of the oncogene modifies the epigenome to prime leukemia development by establishing a new pathological tumoral cellular identity. This epigenetic priming may remain latent until it is triggered by either endogenous or environmental stimuli. This new view on the making of leukemia not only reveals a novel function for oncogenes, but also provides evidence for a previously unconsidered model of leukemogenesis, in which the programming of the leukemia cellular identity has already occurred at the level of stem cells, therefore showing a role for oncogenes in the timing of leukemia initiation.

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Session 2: Genetic and epigenetic factors

A rare RAD21 mutation in a family with history of cancer

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Introduction: Current studies proof an involvement of germline predispositions in the development of around 5% of childhood leukemias (Zhang J et al., NEJM, 2015), although their actual contribution is believed to be much higher. Being able to understand tumor evolution starting from a predisposed cell, opens up new possibilities in the form of disease prevention rather than treatment. Moreover, identified pathogenic germline variants, particularly in ubiquitously expressed genes, might considerably affect a patient's treatment response and treatment related toxicity. However, to reveal the full spectrum of disease relevant germline variants, individualized genomic patient analyses, in the context of the respective familial background (Trio-calling), are needed. Here we confirm the usefulness of this approach on the example of a family with multiple cancer cases.

Methods: Whole exome sequencing (WES) of germline material of the patient and its parents was carried out to identify predisposing germline variants.

Results: The analyzed family showed a strong cancer history, presenting a 13-year-old boy with T-cell acute lymphoblastic leukemia, its father who died due to breast cancer at the age of 41, as well as a grand-father with lung cancer. Due to the different cancer types present within the family, the dysregulation of a ubiquitously expressed gene seemed likely. Utilizing Trio-calling based on WES we identified a rare heterozygous germline mutation P298S (rs148308569, MAF<0.01) in the double-strand break repair protein RAD21. RAD21 is a member of the cohesin complex, which not only controls post-replicative DNA-repair, but is essential for proper chromosome segregation and the prevention of inappropriate recombination between repetitive regions. The presence of the mutation could be verified in both germline and tumor sample of the patient as well as its father, while the variant was absent in the healthy mother. RAD21 P298S is located in the interaction domain of RAD21 with two additional cohesion complex genes (WAPL and PDS5B) and therefore likely to disturb protein-protein-binding relevant for proper chromosome segregation. In addition, disturbed DNA-repair after radiation induced double-strand-breaks mediated through RAD21 P298S is supported by the patient's treatment response, with a seizure after cranial irradiation as well as a cardiomyopathy after the end of intensive therapy.

Conclusion: Trio-calling presents a strong tool in pediatric oncology to identify potentially disease-causing variants, which not only predispose to cancer development but also influence treatment responses. In the future, these variants could lay the basis to predict therapy related toxicities.

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Session 3: Role of the immune system

Maternal infections during pregnancy and childhood leukaemia: A systematic review of previous evidence and a pooled analysis from six international birth cohorts

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Background: Recent evidence strongly suggests that a significant fraction of childhood leukaemias originate *in utero*. Infections during pregnancy which may be transmitted to the foetus, can cause genetic and immunological abnormalities and may lead to childhood leukaemia. Over quite a lengthy period many epidemiologic studies have examined the association of maternal infection during pregnancy and childhood leukaemia risk in the offspring, the results however inconsistent.

Objectives: We aimed to summarize existing evidence on associations between maternal infections and childhood leukaemia and test the associations using prospectively collected data from international birth cohorts.

Methods: We firstly conducted a systematic review to identify studies that reported associations of at least one measure of maternal infection during pregnancy with acute lymphoblastic leukaemia (ALL) or all childhood leukaemias (CL) in the offspring. Random-effects meta-analyses were used to pool odds ratios (OR) of specific type of infection on ALL and CL. Further, we pooled data for 312,879 mother-child pairs (167 CL and 129 ALL cases) from six population-based birth cohorts in the International Childhood Cancer Cohort Consortium (I4C). Data on maternal infections were collected using self-report questionnaires, interviews or medical records, depending on the cohort. Associations between various types of maternal infection and CL and ALL were examined using multilevel Cox proportional hazards models among cohorts with available infection data. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Results: In the systematic review and meta-analysis of previous studies, we found that influenza during pregnancy was associated with higher risk of ALL (pooled OR [95% CI, 3.64 [1.34, 9.90]; number of studies, n=4) and CL (1.77 [1.01, 3.11]; n=6). Varicella (10.19 [1.98, 52.39]; n=2) and rubella (2.79 [1.16, 6.71]; n=3) infections were also associated with higher CL risk. In the pooled analysis of I4C data, influenza during pregnancy was associated with higher, but not statistically significant, risk of CL (HR [95% CI], 1.36 [0.70, 2.64]; n=4) and ALL (1.33 [0.63, 2.80]; n=4). On the other hand, any respiratory infection during pregnancy (1.48 [1.05, 2.09]; n=5) and urinary tract infection (1.68, [1.08, 2.62]; n=6) were associated with higher CL risk; results of these two infections for ALL were similar but with wider CIs.

Conclusions: Maternal infection during pregnancy may be associated with higher risk of childhood leukaemia, but the heterogeneity across studies is high and the evidence is still inconclusive. Future studies with larger sample size, including a greater collection of prospective evidence, and more accurate methods for infection measurements (e.g. biospecimens or medical records) are needed to confirm our findings.

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Session 3: Role of the immune system

Inflammation favors ETV6-RUNX1 positive pre-leukemia in a model of bone marrow niche

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The ETV6-RUNX1 (E/R) fusion gene, arising in utero from t(12;21), is the most frequent alteration in childhood acute lymphoblastic leukemia (ALL). However, E/R is insufficient to overt disease since it generates a clinically silent pre-leukemic clone which persists in the bone marrow but fails to out-compete normal progenitors. Conversely, pre-leukemic cells show increased susceptibility to transformation following additional genetic insults. Infections/inflammation are the most accredited triggers for mutations accumulation and leukemic transformation in E/R+ pre-leukemic cells. However, how E/R and inflammation interact in promoting leukemia is still poorly understood.

We demonstrated that IL6/TNFα/ILβ pro-inflammatory cytokines cooperate with bone marrow (BM)-mesenchymal stromal cells (MSC) in promoting the emergence of E/R+ Ba/F3 over their normal counterparts by differentially affecting their proliferation and survival. Moreover, IL6/TNFα/ILβ-stimulated BM-MSC strongly attract E/R+ Ba/F3 in a CXCR2-dependent manner. Interestingly, E/R-expressing human CD34+IL7R+ progenitors, a putative population for leukemia initiation during development, were preserved in the presence of BM-MSC and IL6/TNFα/ILβ compared to their normal counterparts. Finally, the extent of DNA damage and activation-induced cytidine deaminase (AID) expression increases within the inflamed niche in both cell type, potentially leading to transformation in the apoptosis-resistant pre-leukemic clone.

Overall, these data provide new mechanistic insights in childhood ALL pathogenesis.

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Session 3: Role of the immune system

B-cell identity as a metabolic barrier against malignant transformation

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Obese children and children with type 2 diabetes mellitus (T2DM) have inferior clinical outcomes in B-lineage acute lymphoblastic leukemia (B-ALL) in comparison to children with normal glucose and insulin levels (Butturini et al., 2007; Gelelete et al., 2011; Orgel et al., 2014). Interestingly, fasting has been shown to selectively inhibit the development of B-ALL, but not myeloid leukemia (Lu et al. 2017), suggesting that cell lineage identities (e.g. B-lineage vs. myeloid) are linked to distinct metabolic states in hematopoietic malignancies. B-lymphoid transcription factors (e.g. PAX5, IKZF1) are critical for early B-cell development and commitment to B-cell identity. However, B-lineage leukemia clones frequently carry genetic lesions of these transcription factors. Despite the high frequency, the significance of these lesions has only recently been studied. Here, we discuss the unexpected function of B-lymphoid transcription factors as a metabolic barrier against malignant transformation of B-cell precursor cells. Our recent findings suggest that B-lineage identity is coupled to a specific metabolic state, and that B-lymphoid transcription factors mediate a transcriptional program for restriction of glucose and energy supply to levels insufficient for transformation.

B-lineage and myeloid leukemia cells arise from lesions affecting oncogenes (e.g. *BCR-ABL1*, *RAS*, *MYC*, *MLL*) in multipotent progenitor cells. While they are often transformed by the same oncogenes, B-lineage and myeloid leukemia cells have distinct clinical and biological characteristics. For instance, compared to myeloid leukemia, B-ALL cells carry half the number of mitochondria with about one-third of the mitochondrial volume observed in myeloid leukemia cells. Similarly, while myeloid leukemia cells have abundant ATP reserves (low AMP:ATP ratios), AMP:ATP ratios are high in B-ALL cells, indicating a state of chronic energy deficit in B cell precursors (Chan et al., 2017). Combining ChIP-seq and gene expression studies, we identified a novel B-lymphoid transcriptional program for repression of glucose uptake as well as utilization (*INSR, GLUT1/3/6, HK2/3, G6PD*) and activation of glucose transport inhibitors, including *NR3C1* (glucocorticoid receptor), *TXNIP* (glucose feedback sensor), *CNR2* (cannabinoid receptor). Reconstitution of PAX5 or IKZF1 in patient-derived B-ALL cells lacking functional PAX5 or IKZF1 suppressed glucose uptake, reduced ATP levels and enforced a state of chronic energy deprivation, activating the energy-stress sensor LKB1-AMPK. In contrast, CEBPα-mediated B-to-myeloid reprogramming resulted in transcriptional activation of multiple mediators of glucose uptake/metabolism and energy supply (*Insr*, *Glut1*, *Glut6*, *Hk3*, *Pygl* and *G6pd*). Furthermore, B-to-myeloid reprogramming salvaged chronic energy deficit, restoring a state of energy abundance marked by increases in glucose uptakes and ATP levels (Chan et al., 2017).

Mechanistically, a CRISPR/Cas9-based genetic screen of PAX5-transcriptional targets identified the glucose transport inhibitors NR3C1, TXNIP and CNR2 as central effectors of the tumor suppressive function of PAX5. Inducible reconstitution of PAX5 in patient-derived B-ALL cells lacking functional PAX5 led to depletion of cells in competitive-growth assays. In contrast, CRISPR/Cas9-mediated deletion of *NR3C1*, *TXNIP* or *CNR2* resulted in substantial survival advantage. Genetic ablation of *Nr3c1*, *Txnip* or *Cnr2* increased glucose uptake and ATP levels in murine B-ALL cells, supporting their role as negative regulators of glucose uptake. Transport-independent lipophilic methyl-conjugates of pyruvate and TCA cycle metabolites (dimethyl succinate and oxaloacetate) rescued patient-derived B-ALL cells from PAX5- or IKZF1-induced cell death, and bypassed the metabolic gatekeeper function of PAX5 and IKZF1 in enabling leukemic transformation of B-cell precursor cells expressing *BCR-ABL1* from a conditional knocking allele.

In summary, the high frequency of genetic lesions observed in B-lymphoid transcription factors in B-ALL takes on new significance from our unexpected findings that B-lymphoid transcriptional program restricts glucose and energy supply, functioning as metabolic gatekeepers against malignant transformation of B-cell precursor cells.

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Session 3: Role of the immune system

Commensal gut microbiota protects from infection driven acute lymphoblastic leukemia

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The link between infections and childhood B-precursor Acute Lymphoblastic Leukemia (pB-ALL) was proposed more than 100 years ago. The first biological evidence supporting this hypothesis came up just a few years ago in genetically predisposed pB-ALL mice. These in vivo models corroborate that postnatal infections can trigger pB-ALL. The leukemia arising in these mice are phenotypically and genetically similar to the human counterpart. Hence, these models are key tools to understand the aetiology of the disease. Now we are trying to understand the mechanism by which natural exposure to common infections triggers the disease with the ultimate goal of trying to identify potential preventive strategies.

Modifications of the tissues homeostasis due to alterations in the microbiome can lead to inappropriate activation of the immune system and is associated with numerous diseases caused by infections. Thus, we have analyzed the host-gut microbiome of Pax5+/- mice housed in a specific-pathogen-free (SPF) facility and mice housed in a conventional (pathogen-containing) facility (CF). We used wild type (WT) mice in both housing conditions as a control. As expected, fecal microbiome of SPF housed mice is significantly less diverse than the microbiome of CF housed mice; this holds for Pax5+/- and WT mice. Moreover, we identified community differences between genotypes (Pax5+/- and WT). We also performed co-housing of both genotypes in both environments (CF and SPF). To determine the contribution of intestinal microbiota to pB-ALL development, we depleted it at the time of infection exposure in Pax5+/- mice by treating them with an antibiotic cocktail. Surprisingly, the incidence of the disease increased 3-fold (from 21,95% in Pax5+/- not treated to 62.96% in the Pax5+/- treated mice). The microbiome dysregulation does not modify the number of B cells in the Peyer's Patches but reduced the number of CD3-T cells. Furthermore, we explored the role of T cells in infection driven pB-ALL by studying pB-ALL development in susceptible mice without T cells (Pax5+/-; nu/nu). Under this scenario, the pB-ALL development is not altered, highlighting that T cells do not have a driving role in pB-ALL under infections environments.

In conclusion, our data show that Pax5+/- mice have a different gut microbiome compared to wild type mice and it might function as a barrier against infection driven leukaemia development. Gut commensal bacteria are important for promoting normal host physiology and its alteration might open up routes to develop strategies leading to the prevention of the disease.

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Session 3: Role of the immune system

The role of extracellular vesicles in ionizing radiation-induced bone marrow pathologies

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Bone marrow (BM) is a particularly radiosensitive organ; haematological malignancies, myelodysplastic syndrome and chronic bone marrow insufficiency are considered long-term consequences of bone marrow irradiation. Ionizing radiation (IR) damages the stem and progenitor cells and alters signalling between the stem cell compartment and the BM stroma. The major objective of our work was to investigate extracellular vesicles (EVs) mediated IR effects in the BM and stroma at low and high irradiation doses and to study possible underlying mechanisms using an in vivo murine model.

In order to study the role of EVs in mediating radiation-induced non-targeted effects, BM-derived EVs were isolated from irradiated mice and injected into non-treated animals. Phenotypical changes in the stem cell compartment and stroma, as well as apoptosis, DNA damage and oxidative stress were studied in both directly irradiated and EV-receiving mice. EV transfer induced changes in the BM stem cell compartment similar to the directly irradiated mice and several of the changes were persistent at least 3 months after treatment. Stroma was less affected.

In conclusion, we showed that EVs can transmit radiation damage in the bone marrow and this raises the possibility that they are involved in the development of IR-induced haematological malignancies.

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Session 3: Role of the immune system

Ionizing radiation induces AML related changes in the cargo of extracellular vesicles from haematopoetic system

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Introduction
Induction of acute myeloid leukaemia (AML) is highly associated with radiation exposure. Radiation-induced damage to the hematopoietic stem cell pool is a major driver in the disease, but communication between the tumor and its environment also contribute to the development of the disease. Extracellular vesicles (EVs) are small membrane coated bodies released by the cells into extracellular medium. They have an important role in intercellular communication by carrying proteins and nucleic acids. Using an in vivo model, we have recently demonstrated in the hematopoietic system that EVs can mediate radiation-induced bystander effects, such as DNA damages, chromosomal aberrations or phenotypical changes. Here we investigate the mechanisms of these functional changes, specifically the uptake and the miRNA cargo of EVs from bone marrow of irradiated mice, and the possibility that EVs might transmit AML-related signals.

Methods
We isolated EVs from bone marrow (BM) of total body irradiated mice, labeled them with a selective RNA stain and co-incubated them in vitro for 3 hours with BM cells extracted from irradiated or control mice. We quantified the uptake of EVs in different BM subpopulations by flow cytometry and fluorescence microscopy.

To test how in vivo irradiation affects the miRNA cargo of EVs, total RNA was isolated from the same EVs, subjected to miRNA profiling and assessed by bioinformatical tools. Significantly altered miRNAs were validated by qRT-PCR in EVs, BM cells of recipient and donor mice.

Results
There are differences in EV uptake capacity of different BM cell subpopulations. Irradiation changed the extent of EV uptake capacity of different subpopulations. We identified a panel of miRNAs differentially expressed in the EVs following TBI of mice with involvement in DNA damage repair, immune system regulation and AML. Expression of miRNAs in EVs not always follows the expression in the donor cells.

Conclusions
EVs transmit certain radiation related signals; IR alters the miRNA cargo of EVs. The altered miRNA cargo might contribute to the development of radiation induced AML. IR changes the EV uptake capacity of recipient cells which can also contribute to AML development.

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Bundesamt für Strahlenschutz

Poster Session

TCF3-PBX1 can arise prenatally

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Pediatric acute lymphoblastic leukemia (ALL) is characterized by recurrent preleukemic chromosomal translocations that frequently emerge in utero. The translocation t(1;19), resulting in the formation of the chimeric transcription factor TCF3-PBX1, is the second most frequent structural aberration occurring 5-10% of B cell precursor patients. The TCF3-PBX1 fusion is commonly believed to originate postnatal, even though evidence for a prenatal origin has been found in in some cases.

We therefore screened the umbilical cord blood (UCB) of 340 healthy newborns for TCF3-PBX1. Previous studies used RNA to screen for fusion transcripts. However, the instability of RNA used as the target for prevalence exploration and the low expression of the RNA transcripts in preserved cord blood samples hindered the analyses. Hence, we developed a new DNA based screening method: genomic inverse PCR for exploration of ligated breakpoints (GIPFEL). GIPFEL allows for the detection of chromosomal translocations on DNA level without prior knowledge of the position of the breakpoint. GIPFEL screening of 340 UCB samples for TCF3-PBX1 showed the fusion gene to be present in two newborns (~0.5%).

In a previous study, the TCF3-PBX1 fusion transcript was shown to be present in dried blood spots of two newborns who later developed B-ALL. As our study was retrospective, we were unable to see whether our TCF3-PBX1 positive cases developed B-ALL later in life. However, the relatively high percentage of carriers hints at the possibility of healthy carriers and a low penetrance, comparable to ETV6-RUNX1.

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Session 4: Environmental risk factors

New Results from the Childhood Leukemia International Consortium (CLIC)

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The Childhood Leukemia International Consortium (CLIC) has been officially established in 2007, originating from an initiative of case-control study investigators from Australia, Canada, France and the USA, and until today has grown to include >25 investigators of >30 studies and has a successful track record of >15 publications and further ~20 ongoing or proposed pooled analyses. The mission of CLIC is i) develop and support collaborations between scientists involved in childhood leukaemia research to accelerate knowledge on factors that influence the risk of leukaemia through epidemiological studies and related research; ii) encourage free exchange of results (published or unpublished) and ideas in a collegial environment without fear of competition, iii) promote research opportunities and career development of junior investigators in the field.

CLIC studies are of case-control design and most of the earlier members were interview-based case-control studies from dominantly Europe, North America and Australia, some of them having had contact already during their design phase and hence some pooling projects were straight forward. Over time, CLIC was successful of including studies also from other parts of the world, notably Latin America, some from Asia, and Egypt, and is endorsing the need for more studies from this under-researched part of the world. More recently, some entirely registry-based nested case-control studies from the Nordic countries and from the USA joined CLIC which now allows also some methodologically-oriented sensitivity analyses when comparing interview-based studies with mostly exhaustive exposure information but the need for assessing potential impact of reporting or selection bias with the nationwide studies with rather limited exposure information. CLIC covers a large time period with some studies from as early as the 1970s and very recently conducted studies, allowing examination of calendar time in possibly time-varying risk factors. Not all but many CLIC studies did collect or have access to biological specimen. In total, CLIC has data on more than 40,000 cases with childhood leukaemia, enabling CLIC to look into how risk compares across subgroups, including sex, age, leukaemia type, geography and other study features.

Inherent in the CLIC setup is that pooled analyses are on factors that have been investigated and often published by the original studies. Hence, the value is the increased sample size to investigate subgroups and sometimes more opportunities to look at more complex exposure-response relationships. For other factors some but not all CLIC studies have published, hence with the CLIC approach potential publication bias can be reduced and with adding more diversity new insight into geographical variation of potential risks can be assessed.

At the conference an overview of CLIC results will be presented and putting those results into the context of where we stand with uncovering the causes of childhood leukaemia. CLIC is in the process of expanding to CLIC+, including case-control studies of other childhood cancers than leukaemia.

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Session 4: Environmental risk factors

Current research and future opportunities in the International Childhood Cancer Cohort Consortium

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Background

The International Childhood Cancer Cohort Consortium (I4C) has assembled the first dataset consisting of prospective measurement of exposures during pregnancy and childhood together with biospecimens and occurrence of cancer in childhood.

Recent publications and related future research

We have used the available dataset on 388,000 mothers and babies, among whom 700 childhood cancers have already occurred, to investigate hypotheses that have emerged during the previous fifty years of research on causes of childhood cancer. Importantly, we have been able to confirm that large babies have a higher risk of childhood cancer, with an estimated 26% increase in risk for each 1kg increase in birth weight. This is an important clue to the aetiology of childhood cancer. What has not been possible to examine with the previous retrospective datasets is to investigate which biological pathways leading to higher birth weight might be the ones that are the major determinants of the increase in risk of childhood cancer. We are currently investigating epigenetic markers that might be associated with both birthweight and cancer and have plans to compare metabolomic profiles in children who develop cancer, to cohort controls.

Focusing on factors related to birthweight, we have also found that one of those that is most important in this regard, birth order, is not only related to risk of childhood cancer – first born babies being at highest risk – but that birth order appears to interact with birth weight to determine risk. The interaction is further influenced by the age of the father. There are several possible explanations for this that we will be exploring further.

Finally, in collaboration with the Norwewith the Cohort Study (MOBA) we are planning to examine viral DNA in cord blood to determine whether we can identify maternal infection, passed on to the fetus in this way. A comparison between the measured virome in cord blood of childhood cancer cases and cohort controls will also be made.

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Bundesamt für Strahlenschutz

Session 4: Environmental risk factors

Space-time Clustering of Childhood Leukaemia: A Systematic Review and Pooled Analysis

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Childhood leukaemia (CL) is the most frequent paediatric cancer but its aetiology remains largely unknown. It has been proposed that infections might play a causal role, but no specific pathogen has been implicated to date. The 'population mixing' hypothesis suggests that leukaemia may be a complication of a specific infection yet to be identified, while the 'delayed infection' hypothesis suggests that in some children a lack of exposure to common childhood infections in the first years of life may lead to an abnormal immune response to later infections resulting in leukaemia. In both scenarios, the incidence of CL might vary in time and space, reflecting the circulation dynamics of these infectious agents. Conversely, epidemiological evidence of space–time clustering would lend support for a causal role of infections. A meta-analysis of space-time clustering studies synthesizing the evidence for different age groups and for different spatial and temporal scales might provide hints about windows of susceptibility and possibly even the likely range of putative aetiological agents. Statistical tests of space-time clustering were first developed as early as the 1960s and used to analyse the incidence of CL. The most common statistical test that has been used is the Knox test for space-time interaction. We performed a systematic review and propose a method for pooling studies using the Knox test for a synthesis of this evidence.

Methods
We searched Embase and MEDLINE for population-based studies that covered a pre-defined study area, included cases under 20 years of age, performed a statistical test of space-time clustering, and were published before July 2016. In order to pre-empt false positives due to multiple testing, we extracted all space–time clustering tests and calculated the proportion of positive tests for each original study and took the mean proportion of significant tests (MPST) at the 5% significance level across studies. In the absence of space-time clustering, the expectation of MPST is 5%. In pooled analyses, we performed a Knox test of the number of pairs of cases close to each other in time and space pooled across studies. We performed separate analyses for residence at time of birth and diagnosis for different combinations of spatial and temporal lags as well as for different age subgroups (0-5, 5-15 years).

Results
47 studies met our eligibility criteria, 25 of which reported Knox tests. The overall proportion of positive tests was higher than expected by chance at both time of diagnosis (26%) and birth (11%). Strong evidence of space-time clustering was found for children under five years of age at time of diagnosis: the mean proportion of significant tests across 12 studies was 26% and the pooled Knox test revealed a relative excess of close pairs of cases of 5.2% ($p < 0.001$). The pooled analysis showed strongest evidence of clustering for a spatial and temporal lag of 5 km and 6 months, respectively ($p < 0.001$). For the age group 5–15 years both MPST and the pooled analysis using residence at diagnosis were suggestive of a deficit rather than an excess of close pairs. No evidence of space–time clustering for age subgroups was found at time of birth. Results from studies of cases of ALL were broadly similar.

Conclusion
The current systematic review suggests that cases of CL cluster in space-time due to an aetiological factor affecting children under 5 years of age. The observed pattern of clustering of children at a young age but closer to the time of diagnosis is compatible with Greaves' 'delayed infection' hypothesis.

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Special Session: Background radiation

An update on the study of childhood cancer and natural radiation in Great Britain

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The published Phase I Study (Leukemia 27 3-9 2013)
This was a register-based case/control study of childhood cancer and two components of natural background radiation: gamma-rays (with directly ionizing cosmic rays) and radon. Cases (n=27447; 9058 leukaemias) were born and diagnosed in GB 1980-2006. Controls (n=36793; two controls per case from 2000) were selected from the same birth register as the case. Gamma-ray exposures were estimated as the mean for one of 459 County Districts (CDs), based on 2283 total measurements. Odds Ratios for associations between leukaemia and cumulative gamma dose, birth to diagnosis were significantly elevated (p=0.01). For gammas and cancers other than leukaemia and for radon with both these disease groupings, ORs were above one, but not close to statistical significance.
The main shortcoming of this Phase 1 GB Study was that, because cases and controls were matched on Birth Registration District, almost half the cases were born in the same CD as their control(s) and have the same dose-rate estimate.

What's new in Phase II of GB Natural Radiation Study?
1) Almost twice as many cases because of an extended calendar period, 1962 to 2010.
2) More parameters for analysis
Census data (Carstairs SES score components; urban/rural status, Population density); variants on geological codings; approximate indicator of Pre/Post-1940 construction.
3) More precise gamma ray estimates for individual locations

Now possible because of an enlarged set of measurements: 10199 instead of 2283, thanks to measurement data made available by the UKCCS investigators.

Investigations to develop better gamma estimates

First Investigation REB 2016 55 103-124
This explored a number of ad hoc models:
- Means over geological or administrative areas
- Distance weighted mean of nearest measurements to the point of interest
We also constructed an optimal linear combination of these results (the "E-OLS" model).
We also used a Gaussian-Matérn ("GM") geostatistical model in which an underlying spatial variation using 16-level bedrock classifications was modified by a Gaussian stochastic process with Matérn correlation structure.
The E-OLS model performed better than the GM (Mean Square Error, "MSE", 371 and 411 respectively). However, the E-OLS predictive errors are not likelihood based and so unreliable

Second Investigation JER 2016 164 300-31
This explored Multi-resolution Gaussian Process models (MRGP) and also four variogram based parametric spatial models. MRGP did best of these but not as well as E-OLS described above. It transpired that errors for the MRGP models could not be calculated which greatly reduced their attraction.

Third Investigation REB 2018 57 321-47
Our third exploration of methods for estimating indoor gamma-ray dose rates at unmeasured locations took advantage of the extra census and other parameters that had become available.
Most of the models described above were re-tested with the enhanced set of parameters. Significant improvements over previous models resulted, with the most promising results from the E-OLS (MSE=356) and GM (MSE=402) models.

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Bundesamt für Strahlenschutz

Special Session: Background radiation

Ecological association between residential natural background radiation exposure and the incidence rate of childhood central nervous system tumors in France, 2000–2012

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High-dose ionizing radiation is an established risk factor for childhood central nervous system tumors (CNST) but the role of low doses remains debated. In particular, there are few studies of natural background radiation (NBR, gamma radiation and radon) and childhood CNST, and their results are inconclusive. This study aimed to investigate the ecological association between NBR exposure and childhood CNST incidence in France.

Incidence data were provided by the French national registry of childhood cancers, which has high completeness. We included 5,471 childhood CNST cases registered over the period 2000-2012. Municipality NBR exposures were estimated by cokriging models, using NBR measurements and additional geographic data. The incidence rate ratio (IRR) per unit variation of exposure was estimated with Poisson regression models. NBR exposures were considered at the time of diagnosis, and cumulatively from birth to diagnosis. In an exploratory analysis, the total brain dose due to NBR was used.

Overall, there was no association between NBR exposure and childhood CNST incidence (IRR = 1.03 (0.98,1.09) per 50 nSv/h for gamma radiation, and IRR = 1.02 (0,96,1.07) per 100 Bq/m3 for radon). An association was suggested between pilocytic astrocytomas and gamma radiation (IRR = 1.12 (1.00,1.24) per 50 nSv/h) but not with radon (IRR = 1.07 (0.95,1.20) per 100 Bq/m3). Upward trends for this CNST subtype were also suggested with the cumulative exposures to gamma radiation and the total brain dose. NBR exposure was not associated with other CNST subgroups (ependymomas, embryonal tumors, and gliomas other than pilocytic astrocytomas). Adjustment for socio-demographic factors did not change the findings.

Conclusions: Our study was based on high quality incidence data, large numbers of CNST cases, and validated models of NBR exposure assessment. Results suggest an association between gamma radiation, as a component of NBR, and pilocytic astrocytomas incidence in France.

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Bundesamt für Strahlenschutz

Special Session: Background radiation

Background Ionizing Radiation and the Risk of Childhood Cancer: A Census-Based Nationwide Cohort Study - New Results from Switzerland

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Antonella Mazzei, Christophe Folly, Christian Kreis, Ben Spycher | Institute of Social and Preventive Medicine, University of Bern

Exposure to high doses of ionizing radiation is an established risk factor of childhood cancer. The general population is commonly exposed to low doses of radiation (<100 mSv) from natural background radiation but the cancer risk associated with this dose level remains uncertain. We investigated whether the incidence of childhood cancer was associated with exposure to background radiation from terrestrial gamma and cosmic rays using data from the Swiss National Cohort (SNC), a nationwide census-based cohort study. We included all children <16 years of age registered in the Swiss national censuses (1990, 2000, 2010-2014) and identified all incident cancer cases from the Swiss Childhood Cancer Registry. The follow-up period lasted until the end of 2014. We used a hierarchical Bayesian model to predict dose rates from terrestrial and cosmic radiation at children's place of residence and estimated hazard ratios in time-to-event analyses using Cox regression models adjusting for sex and year of birth. We included 3,381,347 children and identified 2,959 cancer cases, of which 900 were cases of leukemia, 465 lymphoma, and 669 tumors of the central nervous system (CNS). Hazard ratios per 100 nSv/h dose rate of external radiation were 1.41 (95% CI: 1.11, 1.78) for any cancer, 1.18 (0.77, 1.83) for leukemia, 1.38 (0.76, 2.49) for lymphoma, and 1.53 (0.94, 2.49) for CNS tumors. Adjustment for potential confounders had little effect on the results. Our findings suggest that background radiation may contribute to the risk of cancer in children, particularly CNS tumors. Our findings are consistent with a previous study in Switzerland.

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Session 5: Looking around and forward – what to do next?

Variations and trends in incidence of lymphoid leukaemia in children: Results from 131 population-based cancer registries around the globe

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Background: Lymphoid leukaemia (LL) is the most frequent cancer type in children aged 0-14 years, accounting for approximately 25% of all diagnosed childhood cancers in economically developed countries. The aetiology of LL remains largely unknown. Many studies targeted lifestyle or environmental pollutants as possible risk factors, but with inconsistent results to date. Describing incidence patterns and identifying geographical differences is informative for aetiological research but estimating childhood LL incidence globally is hampered by a lack of reliable data, particularly from resource-poor countries. Using the most up-to-date data collected for the International Incidence of Childhood Cancer (IICC) project we analysed global incidence of childhood LL to promote aetiological research.

Methods: We used incidence data collected in all 131 registries in 65 countries and territories around the globe which were able to provide high quality data for each calendar year in the period 2001-2010 for children diagnosed with LL before the age of 15 years. The analyses by age, gender, and geographical region were complemented by assessment of temporal change in incidence by using comparable data covering (roughly) the decade of the 1980s.

Results: The overall age-standardized incidence rate (ASR) for the entire decade of 2001-10 was 34.8/million person-years based on 68,705 cases. The highest age-specific rate was observed in children aged 0-4 years (52/million). Incidence rates varied substantially between and within the described regions. While the highest incidence was seen in Umbria in Italy (59.1/million), the lowest overall rate was observed in Sub-Saharan Africa (7.9/million), where ASRs ranged from 6.5/million in Kyadondo (Uganda) to 28.5/million in Reunion (France). Compared with the 1980s, the global ASR has increased from 30.4 (95% CI 30.0-30.8) to 34.8/million person-years (95% CI 34.5-35.1). The increase was seen in virtually all compared regions; it was particularly pronounced in Sub-Saharan Africa and North Africa, where the ASR has doubled. However, we also observed a substantial incidence increase in South America, in the Asian regions and in Eastern Europe.

Conclusion: The observed geographical and temporal incidence patterns suggest a link of the LL incidence with socioeconomic development of a population, which may play a role for both aetiology and clinical detection of this malignancy. The increasing trends across regions require further monitoring.

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