CHILDREN WITH CANCER UK

Children with Cancer UK Conference:
Embracing Research, Collaboration & Change
Birmingham, 19-20 September 2023

Book of Abstracts

CHILDREN WITH CANCER UK

Children with Cancer UK Conference:
Embracing Research, Collaboration & Change
Birmingham, 19-20 September 2023

Contents

Embracing research, collaboration and change: Welcome to the Childhood Conference 2023

For Childhood Cancer Awareness Month, we're re-launching our research conference, focusing on Embracing Research, Collaboration and Change this September.

As a charity we are proud of our 35-year legacy and are committed to funding innovative research which has the needs of children, teenagers, young people and their families at the forefront. This year we began a new chapter as we refreshed the look and feel of our charity and ushered in the start of a bold new era for Children with Cancer UK. The fresh new look introduces two arms in an embrace – signifying the breadth of our purpose as a charity, embracing research alongside the wellbeing of children and their families, raising public awareness and recognising the collaborative approach we take with a huge range of organisations. Ultimately, it reflects our role in providing hope and support for the future.

As we embrace a new look, our hope for this conference is to focus on how we hope to embrace change in an ever evolving research landscape, embrace innovation with the research we fund, embrace collaboration with research partners & stakeholders and embrace the future of patient care & quality of life along with empowering the next generation of researchers.
The conference aims to unite leading researchers, clinicians, healthcare professionals, early career researchers, representatives from funders across the childhood cancer sector and patient advocates to share learnings and discuss the latest trends in the field.

The conference will cover a broad range of topics, including genomic medicine, precision medicine, immunotherapy, survivorship care, and more.

In addition to our invited speakers, we have poster presentations, some from early career researchers for whom this will be the first time they have presented their research. Together, all of these conference contributions testify to the range and depth of the research into factors affecting childhood cancer cause, treatment and survival.

Childhood Cancer Conference 2023 is above all an inter-disciplinary meeting. We hope you will find new connections and new collaborators. We wish you a rewarding and enjoyable stay here in Birmingham.

Christiana Ogunbote
Head of Research

About Children with Cancer UK

We are one of the leading childhood cancer research charities in the UK

Around 4,200 children and young people are diagnosed with cancer every year in the UK. That's around 10 children and young people diagnosed with cancer every day in the UK. We've been working tirelessly since 1988, to fund research and initiatives that support children and their families through their cancer journey.

Thanks to the help of our extraordinary supporters, fundraisers, ambassadors and volunteers, we are creating a future where every child and young person survives cancer.

Jo Elvin, Chief Executive

What we do

We fund research

We believe in the power of science - that's why we pour our fundraising into research. Right now, we're funding over 55 different research projects, enabling scientists and medical experts to develop better, kinder treatments.

We support families

We provide funding for emotional and financial support both in and out of the hospital, allowing families to focus on being there for their children and each other through treatment and beyond – even through the unthinkable loss of a child.

We raise awareness

We help the general public and wider scientific community understand childhood cancer better. Through our initiatives and campaigns we work to ensure that childhood cancer is always on the agenda.

CHILDREN WITH CANCER UK

CHILDREN WITH CANCER UK

Research Strategy

2022–2027

Introduction

At Children with Cancer UK, our vision is a world where every child survives cancer.

We are dedicated to improving survival of all childhood (0 – 14 yrs. old) and young adult (15 – 24 yrs. old) cancers. Over the past thirty years, we have witnessed dramatic improvements in the survival of some paediatric and young person's cancers, yet there are still cancers which have a fatal prognosis. We rely on the generosity of the public to invest in research. As the UK's leading charity dedicated to childhood cancer research, we are proud of our contribution to the ongoing breakthroughs which have saved and improved thousands of young lives.

Research Aims

Our research programme is designed to progress our principal aims.

First, we wish to develop improved treatments so that more patients are cured with less toxic side effects.

Second, we wish to better understand how cancer develops so that one day we may be able to prevent it.

Research Philosophy

Children with Cancer UK is the leading national children's charity dedicated to the fight against childhood cancer. Children, young people, and their families are vital to the research we fund; we therefore urge all applicants to ensure representatives from patients and the public are actively involved from an early stage in research projects. As a charity we are committed to working in partnership with patients and the public, we recognise the valuable insight this involvement can provide.

Children with Cancer UK values its strong and established partnerships with others in the paediatric and young adult cancer community. We seek opportunities to collaborate with organisations which share our vision of helping children and young people in their journey with cancer including other charities, government funders, cancer organisations and universities. We recognise the value of working with others to share experience, minimise costs and thereby maximise the efficient use of charitable funds. Our current partnership with the Association for Medical Research Charities (AMRC), the National Cancer Research Institute (NCRI) and the Children and Young People with Cancer Coalition (CYPCC) have demonstrated the power of what we are able to achieve when our efforts are united.

We also encourage collaboration among the researchers we fund. For example, we have core-funded the Children's Brain Tumour Drug Delivery Consortium and co-funded INSTINCT, a network across three of the UK's leading paediatric neuro-oncology centres working to improve treatments for patients with high-risk childhood brain tumours.

We understand the need to invest in early-career researchers. In future, we hope to support the next generation of clinician scientists and research leaders, champion their long-term career progression through our fellowship and clinical studentship programmes and prepare them to make substantial contributions to improving outcomes for children with cancer.

As a charity, our funding programme has paid particular attention to supporting promising and innovative research areas to provide proof of concept studies which complement the funding of major clinical trials. These studies are usually small in scale but often are essential in enabling researchers to go on to develop proposals for major trials. We have successfully 'seed-funded' research projects that have been a springboard for much wider investigations, leading to discoveries that will ultimately change our understanding of children's cancers and how to cure them. Children with Cancer UK will continue to champion these efforts and has both supported and co-funded important elements of major, ground-breaking clinical trials and significant projects which have considerably contributed to better outcomes for young patients.

Since 1995, Children with Cancer UK has invested in epidemiological research aimed at identifying possible causes of cancer. We have contributed substantial funding to set up the Childhood Leukaemia International Consortium (CLIC) which aims to promote investigations of the role of environmental and genetic risk factors in various sub-types of leukaemia among children. We have also helped to establish a central data collection centre at the International Agency for Research on Cancer (IARC, part of the World Health Organization) from research studies conducted in 12 countries. The ultimate goal of these on-going studies is to identify practicable approaches to cancer prevention.

Current Research Priorities

Development of more effective treatments

We invest in targeted, less toxic treatment options.

In spite of the impressive, improved prognosis for cancer in children and young people seen over the last 50 years, survival has recently plateaued. Moreover, many of those cured suffer significant side effects. We believe that more targeted, less toxic treatment options including immunotherapies and tailored treatments which target cancer-specific molecular changes are an important area for research investment.

Promotion and dissemination of research findings to achieve maximum research impact

We hope to remove some of the barriers faced by researchers when attempting to share the efforts of their work.

We support a new open access publication platform developed by AMRC and its partners called AMRC Open Research. This will help researchers, but also assist clinicians accessing such publications, in order to facilitate the optimal management of the patients they are caring for.

Understanding cellular and molecular oncogenesis

We support research into basic cellular and molecular biology.

Basic cellular and molecular biology research holds the key to understanding the mechanisms through which cancer develops and by implication the development of new therapies. Over the next five years, Children with Cancer UK will continue to support such studies but will give priority to those deemed by our Scientific Advisory Panel (SAP) and Board of Trustees to have a clear translational benefit in the short term.

Identification of improved diagnostic and prognostic biomarkers

Accurate diagnosis and disease monitoring are central to the development of more effective, less toxic stratified therapies.

Strong support for this approach is seen in the application of cytogenetics and MRD in leukaemia's and molecular classification of medulloblastoma, which were previously only research tools but are now firmly embedded as 'standard-of-care' in routine clinical practice. The development of similar approaches in other tumour types is an important area for future research.

Early identification and mitigation of treatment related toxicity

We support clinical and laboratory research aimed at improving survival and quality-of-life.

Toxicity of therapy is an increasingly prominent cause of both short- and long-term morbidity and mortality as there are now more second and subsequent lines of therapy if initial treatment is unsuccessful. We support research seeking to improve understanding of the mechanisms of toxicity which may be used to design future treatment strategies that maintain efficacy yet reduce early and/or late toxicity as well as identifying genetic and other factors which might be used to mitigate this risk.

How we fund research

We welcome all applications which are aligned with our research priorities and objectives as outlined above. We primarily fund, but are not limited to funding, basic laboratory, prospective epidemiological and pre-clinical and clinical research studies. The type of grant and funding we offer will vary within any given grant call and will be determined by both our income and the identified need within the wider research landscape. However, we are committed to supporting:

- Pilot grants (including to support MPhil Studentships as a platform for PhD studentships)
- Project Grants
- PhD Studentships
- Fellowships
- Clinical trials

The full details of the timeline, remit, rationale and eligibility criteria for the call, and the size and types of grants available to applicants, are detailed in tender documents, application forms and guidance notes that are published at the call launch. Project Grants, Fellowships and PhD Studentships Awards are usually annual calls, with a two-stage application process.

The Board of Trustees make the final decision regarding the allocation of funding following recommendation from the SAP and PPI representatives. Both the SAP and Board of Trustees are mindful of recommendations received from government bodies and medical research charities whilst developing the remit of each funding call, to ensure that we can identify and respond to areas of unmet need and have the flexibility to react to current circumstances.

Stage 1

The first stage is submission of a short preliminary application giving an outline of the proposed research – the aims, methods, and the credentials of the research team. Preliminary applications undergo initial internal triage to check that forms are completed correctly, and the proposed research is within the scope of the call. Preliminary applications are then reviewed by the SAP. The most promising applications are taken through to the second stage.

Stage 2

Applicants are invited to submit a detailed proposal. Short-listed Fellowship and Studentship applicants will also be interviewed. Trustees of the charity make the final decisions, based on advice from the SAP and the amount of funding available.

We will no longer be accepting ad hoc grant applications and encourage all applicants to submit an application during the yearly funding calls. We expect to fund at least 50% of applications that progress to Stage 2.

Who will we fund?

Proposals for all grant types must be submitted by a UK academic institution (university, hospital or research institute). We will consider funding international collaborations only where the principal investigator is employed at a UK research institution. The principal investigator will be held responsible for managing the grant, both scientifically and financially, and will be our point of contact. If that is not possible or practical, then please contact us for specific permission to apply.

Peer review

The detailed research proposals are reviewed by external experts, from the UK and/or overseas, selected according to their relevance to the proposed research. External reviewers are asked to assess the detailed research proposals against the following criteria:

- The importance, originality, and relevance of the project
- The study design, including the likelihood of achieving decisive results, and whether the timeline is realistic, the methods are appropriate, if there is sufficient statistical power, etc
- The credibility and justification of the financial request
- The ability of the research team to carry out the proposed work
- Whether the use of animals, if applicable, is adequately justified and aligns with the NC3Rs guidelines for Replacement, Reduction and Refinement
- Whether there are any likely major obstacles that the research team may encounter
- Each external reviewer provides written comments and an overall score, commenting on the originality, importance, design and costing of the proposal. Feedback will be provided to applicants following review by members of the SAP.

How do we support successful grant holders?

The grant can only commence once the Grant Award Letter has been signed by all parties and returned to us. Grants must be started within 12 months from the date on your award letter.

Requests for payment should be delivered according to the award letter in line with the grant budget. Payments will only be made once the award letter has been fully signed and a grant start date has been confirmed.

Throughout the term of the grant, it is vital that we receive reports detailing the progress of the grant and the impact of the research. Unless specified in the award letter, progress reports must be provided annually, with a final report due within three months of the end of the grant. We will support requests to adjust the existing grant budget when required. Continuation of funding is dependent upon the completion of satisfactory progress reports. Failure to submit reports on time will jeopardise the continuation of the Grant.

When will the charity review the research strategy?

We aim to review our research strategy every 3-5 years.
Further enquiries can be made at **research@childrenwithcancer.org.uk**

Conference Organising Committee

Professor Bruce Morland

Bruce Morland has recently retired as a Professor of Paediatric Oncology at Birmingham Women's and Children's Hospital. He spent his career managing children with non-CNS (Central Nervous System) solid tumours and is an international expert in the treatment of liver and bone tumours. He has extensive experience in the development of novel new therapies for childhood cancer and the conduct of early phase clinical trials. He was previously Chairman of the Children's Cancer and Leukaemia Group (CCLG).

Professor Bruce Morland

Professor Pam Kearns

Pamela Kearns is Professor of Clinical Paediatric Oncology at the University of Birmingham and an Honorary Consultant Paediatric Oncologist at Birmingham Women and Children's Hospital.
She is Director of the University of Birmingham's Institute of Cancer and Genomic Sciences and Director of the Cancer Research UK Clinical Trials Unit (CRCTU). She is a Trustee for Cancer Research UK as well as A Child of Mine, a charity dedicated to supporting bereaved parents. She is also Chair of the Research Assessment Panel for GOSH Charity, and Chair of The Independent Scientific Advisory Panel for Bone Cancer Research Trust.

Professor Pam Kearns

Scientific Advisory Panel

The members of our Scientific Advisory Panel freely give their time and expertise to drive forward research in our fight against childhood cancer. This includes assessing research grant applications as part of our peer review process and discussing developments in the field to take forward new initiatives.

Research into childhood cancer is a broad field and we aim to reflect the diversity of topics amongst the membership of our Scientific Advisory Panel. Thus, we select our Scientific Advisory Panel from a pool of experts to tailor for each funding call, depending upon the subject background required. Tenure on the Panel is for up to three years.

Professor Christina Halsey (Chair) Scientific Advisory Panel

Professor Christina Halsey (Chair)

Senior Clinical Lecturer, Institute of Cancer Sciences, University of Glasgow
Dr Christina Halsey is a paediatric Haematologist who combines clinical and academic work. Her research centres on the biology and treatment of leukaemias that have spread to involve the central nervous system (CNS). Current projects include investigating the adaptation of leukaemic cells to CNS and bone marrow microenvironments and identifying metabolic vulnerabilities that can be exploited therapeutically. A second major interest of Dr Christina Halsey's group is in mechanisms and therapeutic strategies that might reduce neurotoxicity associated with CNS-directed treatment in childhood acute lymphoblastic leukaemia. This is linked to development of better biomarkers for CNS leukaemia and identifying children at risk of neurotoxicity who are suitable for targeted interventions. Dr Christina Halsey's research is combined with clinical work at the Royal Hospital for Children, Glasgow, where she cares for children with a wide range of blood disorders and cancer. She also play a major role in several international consortia working to improve outcomes for children with cancer and is leading several clinical studies exploring ways to improve CNS-directed therapy and reduce neurotoxicity of therapy.

Scientific Advisory Panel continued

Dr Yann Jamin

Dr Yann Jamin

Children with Cancer UK Research Fellow, The Institute of Cancer Research, London
Dr Yann Jamin is an expert in molecular and functional imaging applied to cancer. Dr Yann Jamin is a junior group leader at the ICR since 2014 and his research focus on Magnetic Resonance Imaging (MRI). His research used advanced mouse models of neuroblastoma and computer-aided digital pathology to calibrate non-invasive MRI-based functional and molecular imaging scans to reveal and maps regional variations in active disease and to monitor and predict how neuroblastoma respond to therapy. Collaborating with the Royal Marsden Hospital and Great Ormond Street Hospital, he aims to translate these scans into practical solutions to enhance the clinical management of children with neuroblastoma. His goals are to improve radiological diagnosis and response assessment while both shedding new lights on the biology of the disease and accelerating the development of more effective and safer therapies for children with cancer In May 2014 he was awarded a Children with Cancer UK Research Fellowship to help him to take forward these ambitions. Dr Yann Jamin joined our Scientific Advisory Panel in April 2016.

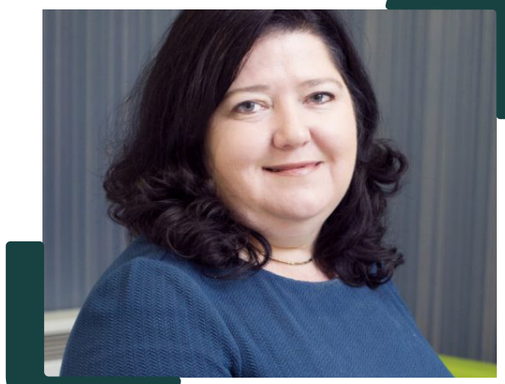
Dr Helen Jenkinson

Dr Jenkinson is a consultant paediatric oncologist at Birmingham Women's and Children's NHS Foundation Trust who looks after all the children referred to and managed by the retinoblastoma service and manages their chemotherapy jointly with paediatric oncology centres around the UK. Her retinoblastoma care is based in the Eye Department and the Oncology clinic. She is also the Clinical lead for the Late Effects Multidisciplinary team and has a major role in the care of long-term survivors of childhood cancer both in the out-patient Oncology clinic (for under 18's) and in the Adult Late Effects Clinic at University Hospital Birmingham (over 18s). Dr Jenkinson's local and national roles include being Chair of the Children's Cancer and Leukaemia Group (CCLG) Late Effects Core Discipline group, Chair of the CCLG Retinoblastoma special interest group, National Clinical Advisor to the National Cancer Survivorship Initiative (NCSI). She is also Chair of the West Midlands Regional Children's Tumour Registry.

Dr Helen Jenkinson

Dr Lynley Marshall

Consultant in Paediatric & Adolescent Oncology Drug Development, The Royal Marsden NHS Foundation Trust; Honorary Faculty/Senior Lecturer, The Institute of Cancer Research, London
Dr Lynley Marshall is a consultant paediatric oncologist and Paediatric Clinical Research Lead at The Royal Marsden Hospital, London. She heads the Paediatric and Adolescent Oncology Drug Development Team, focusing on early phase clinical trials of experimental therapeutics for high-risk, poor-prognosis malignancies (solid and CNS tumours). She undertook her PhD at The Institute of Cancer Research (ICR) in the field of novel targeted therapeutics for paediatric high-grade glioma. She is a Clinical Senior Lecturer in the Division of Clinical Studies at The ICR. She currently chairs the UK's NCRI Children's Group Novel Agents Subgroup and is Clinical Trials Theme Co-Lead for the UK's Paediatric Experimental Cancer Medicines Centre (ECMC) Network. She is a member of the Clinical Trials Committee of the Innovative Therapies for Children with Cancer (ITCC) European early phase clinical trials consortium, and of the Executive Committee of the SIOPE-ITCC ACCELERATE multi-stakeholder platform.



Dr Lynley Marshall

Professor Matthew Murray

Professor Matthew Murray

University Reader and Honorary Consultant Paediatric Oncologist
Professor Matthew Murray works at both the Department of Pathology, Cambridge University and Department of Paediatric Haematology and Oncology, Cambridge University Hospitals NHS Foundation Trust, United Kingdom. He has a research interest in the clinical and molecular aspects of children's tumours, in particular germ cell tumours (GCTs), and was the first to demonstrate the potential utility of specific circulating microRNAs for diagnosis, disease-monitoring and detection of relapse in this disease. He has attracted >£4M of grant funding to date as a Principal and Co-Investigator.

Scientific Advisory Panel continued

Professor Sue Burchill

Professor Sue Burchill

Professor of childhood and adolescent cancer research, University of Leeds, Leeds Professor Sue Burchill graduated with a BSc in Pharmacology (1982) and PhD in Medicine (1986) from the Sunderland School of Pharmacy and the University of Newcastle upon Tyne respectively, before pursuing a translational research career. After post-doctoral research in the University of Newcastle upon Tyne, England and The University of Arizona Cancer Centre, USA she moved to Leeds, England in 1992 to establish the Children's Cancer Research Group at St James's University Hospital in Leeds, where she remains the scientific director. Sue has made major contributions to medical research in the field of cancer in children and young people, her leadership in multi-disciplinary collaborative groups includes shaping international strategies for the evaluation of new targeted treatments to improve outcomes. Her own research is focussed on strategies to detect and eradicate metastatic drug resistant disease that is responsible for progression and relapse in neuroblastoma and bone cancers that affect young people.

CHILDREN WITH CANCER UK

Children with Cancer UK Conference:
Embracing Research, Collaboration & Change
Birmingham, 19-20 September 2023

Agenda

Children with Cancer UK Conference:
Embracing Research, Collaboration & Change
Birmingham, 19-20 September 2023

RCPCH has approved this activity for CPD in accordance with the current RCPCH CPD Guidelines.

Tuesday 19 September 2023

09:00 - 09:55	*Registration and refreshments*	

Embracing Change

10:00 - 10:10	Welcome	Professor Bruce Morland, Professor Pamela Kearns, *University of Birmingham*
10:10 - 10:20	Children with Cancer UK: Ambitions for the future	Jo Elvin, *Children with Cancer UK*
10:20 - 10:30	Childhood Cancer Awareness Month focus	Christiana Ogunbote, *Children with Cancer UK*
10:30 - 11:00	Stratified Medicine Paediatrics - National Molecular Tumour profiling platform for relapsed childhood cancer	Professor Louis Chesler, *Institute of Cancer*
11:00 - 11:20	*Refreshment break*	
11:20 - 11:35	Weaving the web of connections	TBC

Embracing Research

11:35 - 11:55	Developing models to test new drug treatments for childhood leukaemia	Professor Owen Williams, *UCL GOS ICH*
11:55 - 12:15	Engineering the immune system to treat T-cell acute lymphoblastic leukaemia (T-ALL)	Professor Marc Mansour, *UCL GOS ICH*
12:15 - 12:35	Biomarkers and discovery of new therapeutic targets for chemotherapy associated neurotoxicity	Professor Chris Halsey, *University of Glasgow*
12:35 - 12:55	Targeting over-expressed microRNAs in germ cell tumours	Dr Shivani Bailey, *University of Birmingham*
12:55 - 13:15	Paul O'Gorman Fellowship update	Dr Yann Jamin & Dr Zoe Walters *Institute of Cancer Research*
13:15 - 14:30	*Lunch break & poster presentation*	

14:30 - 15:00	Liquid Biopsy: pathways to translation	Professor Matt Murray, *University of Cambridge*
15:00 - 15:20	Vaccine opportunities for the future	Professor Andrew Beggs, *University of Birmingham*
15:20 - 16:05	Global Cancer Challenges: Development, Conflict & Economics	Professor Richard Sullivan, *King's College London*
16:05 - 16:50	Panel discussion Is novel drug discovery enough? – repositioning and repurposing in rare cancers	Dr Lynley Marshall, *The Royal Marsden* Professor Sue Burchill, *University of Leeds*
16:50 - 17:00	*Closing remarks*	Conference Committee
17:00 - 18:00	*Drinks reception and poster exhibition*	
19:00 - late	*Evening dinner, awards and entertainment*	

Wednesday 20 September 2023

08:00 - 09:00	*Registration, refreshments and poster exhibition*	
09:00 - 09:10	Welcome	Professor Morland, Professor Kearns
09:10 - 09:40	Embracing Personal Journeys in the Cancer Community	Ellen Bisci & Ace Manthey
09:40 - 10:00	Patient Reported Outcomes Research: opportunities and challenges	Dr Ameeta Retzer, *University of Birmingham*
10:00 - 10:20	BENCHISTA: Understanding why childhood cancer survival varies between countries	Professor Kathy Pritchard-Jones, *UCL GOS ICH*
10:20 - 10:40	*Refreshment break*	

Embracing Collaboration

	Partners in Childhood Cancer Research spotlight	Christiana Ogunbote
10:40 - 11:10	**Little Hero & Blue Skye Thinking** INSTINCT-MB: Discovery, development, and delivery of effective combination therapies for high risk medulloblastoma	John Rainsbury & Sally Hall; Steve Clifford, *Newcastle University*
11:10 - 11:35	**Cancer Research UK - Innovation awards** Relapse-specific therapeutic vulnerability evaluation in childhood and young adult ALL (REVEALL)	Laura Danielson, Dr Kent Fung, *University College London*
11:35 - 11:50	**Tessa Jowell Brain Cancer Mission** Paediatric Mission	Camille Goetz
11:50 - 12:05	**Children's Cancer and Leukaemia Group** Priorities and collaborations in children's cancer research and beyond	Ashley Ball-Gamble
12:05 - 12:30	**Blood Cancer UK** UKALL 2011	Sarah McDonald, Amy Kirkwood, *University College London*

12:30 - 12:45	**Little Princess Trust**	Phil Brace & Wendy Tarplee-Morris
12:45 - 13:00	**Bone Cancer Research Trust** Partnership to accelerate research into Ewing Sarcoma	Dr Zoe Davison
13:00 - 14:00	*Lunch & poster exhibition*	

Embracing the Future

14:00 - 14:20	Personalised survivorship care: customising support towards unmet psychosocial needs in young people with cancer	Professor Faith Gibson, *University of Surrey*
14:20 - 14:40	A comprehensive surveillance system for adverse health outcomes in British survivors of childhood, teenage and young adult cancer	Professor Mike Hawkins, *University of Birmingham*
14:40 - 15:00	Getting ahead of drug resistance in diffused midline glioma	Professor Chris Jones, *Institute of Cancer Research*
15:00 - 15:40	Mind the Gap: Navigating the landscape as an Early Career Researcher	Dr Yann Jamin
	Rapid Abstract Presentations	
	In vivo modelling recapitulates radiotherapy delivery and late-effect profile for childhood medulloblastoma	Dr Jemma Castle
	Ketogenic diet as a metabolic vehicle for enhancing the therapeutic efficacy of mebendazole and devimistat in preclinical pediatric glioma	Dr Purna Mukherjee
	Genetic or pharmacological inactivation of CREBBP sensitises B-cell Acute Lymphoblastic Leukaemia to Ferroptotic Cell Death upon BCL2 Inhibition	Dr Simon Richardson
	Exploring a potential mechanistic role of CpG-specific methylation in the relationship between environmental exposures and childhood acute lymphoblastic leukaemia	Dr Jessica Saville
	Development of novel small-molecule drug combinations targeting high-risk MYC-driven medulloblastoma	Dr Louisa Taylor
	Targeted inhibition of Bcl-xL in H3K27M-altered diffuse midline glioma is a potent anti-tumour therapy	Dr Ashley Vardon
15:40 - 15:55	How to successfully apply for funding; insights from the 2022 Research Project Grant Call and future opportunities	**Scientific Advisory Panel:** Professor Chris Halsey Professor Sue Burchill Dr Yann Jamin Dr Helen Jenkinson Dr Lynley Marshall Professor Matt Murray
15:55	*Close & refreshments*	Professor Kearns & Professor Morland

CHILDREN WITH CANCER UK

Children with Cancer UK Conference:
Embracing Research, Collaboration & Change
Birmingham, 19-20 September 2023

Abstracts

In vivo modelling recapitulates radiotherapy delivery and late-effect profile for childhood medulloblastoma

Jemma Castle[1], Gary Shaw[2], Dominic Weller[1], Edward Fielder[3], Teklu Egnuni[2], Mankaran Singh[1], Roderick Skinner[1], Thomas von Zglinicki[3], Steven C. Clifford[1], Susan Short*[2], Satomi Miwa*[3], Debbie Hicks*[1].

[1] Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK.
[2] Leeds Institute of Medical Research, Wellcome Trust Brenner Building, St James's University Hospital, Beckett St, Leeds, UK.
[3] Biosciences Institute, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK.
* These authors contributed equally.

Background:

Medulloblastoma (MB) is the most common malignant paediatric brain tumour, with 5-year survival rates over 70%. Survivors frequently suffer a wide variety of late-effects due to their tumour and its treatment. Cranial radiotherapy (CRT) plus posterior fossa boost (PFB) is mainstay of treatment for non-infants and has contributed to increasing survival rates. However, radiotherapeutic insult to the surrounding normal brain tissue has deleterious consequences and increases the risk of endocrine impairment, secondary tumours, neurocognitive (NC) impairment, neuromuscular/neurological (NM/NL) deficits, and premature ageing/frailty. Sadly, approaches to ameliorate radiotherapy-induced late-effects are lacking and a paucity of appropriate model systems hinders their development.

Method:

We have developed an *in vivo* model system that recapitulates the radiotherapy dose, delivery and late-effect profile of childhood medulloblastoma, at an equivalent developmental stage. Consistent with human regimens, age-equivalent (postnatal days 28-37) male C57Bl/6J mice received targeted, CT image-guided, CRT (human-equivalent 38 Gy, n=12) or CRT with PFB (human-equivalent 49 Gy, n=12), via the small animal radiation research platform (SARRP) and were longitudinally assessed for over a year. Late-effects were compared to a sham-irradiated group (n=12).

Results:

CRT was well tolerated, independent of PFB receipt, and no mice suffered severe acute toxicity. Mice were significantly more frail following irradiation (Frailty index; p=0.0002) and had reduced physical functioning; time to fall and grip strength were significantly lower (rotarod; p=0.026 and grip strength; p=0.006, respectively). Neurocognitive deficits were also apparent; irradiated mice displayed significantly worse working memory (Y-maze; p=0.009) and long-term memory (Barnes maze; p=0.029). Receipt of PFB did not induce a more severe late-effect profile.

Conclusion:

We conclude that our *in vivo* model of childhood MB radiotherapy recapitulates the late-effect profile of MB survivors. Our clinically-relevant model will facilitate both the elucidation of novel/target mechanisms underpinning MB late-effects and the development of novel interventions for their amelioration.

Exploring a potential mechanistic role of CpG-specific methylation in the relationship between environmental exposures and childhood acute lymphoblastic leukaemia

Jessica Saville[1], Jill McKay[1], Lisa Russell[2], Kay Padget[1]

[1] Faculty of Health and Life Sciences, Department of Applied Sciences, Northumbria University.
[2] Biosciences Institute, Newcastle University Centre for Cancer, Faculty of Medical Science, Newcastle University.

Background:

The aetiology of childhood acute lymphoblastic leukaemia (ALL) remains unclear. Whilst genetic aberrations have been suggested as initiating events, these alone are not sufficient for disease onset and additional factors likely play a role in leukaemia development. Epigenetic alteration, such as changes in DNA methylation, plays a key role in human health. Our previous gene-level analysis provided evidence suggesting DNA methylation may be a mediating mechanism through which some environmental factors may contribute to ALL manifestation. Here we have used our previously established, meet-in-the-middle approach, to perform in depth CpG-level analysis to investigate DNA methylation as a mediating mechanism between potential risk exposures and ALL.

Method:

We utilised our previously published data and published meta-analysis to identify differentially methylated CpGs (DMC's) associated with environmental risk factors related to ALL. We then selected data from a study measuring DNA methylation in ALL, where DMC's conserved across all ALL subtypes were termed constitutive CpGs. DMCs associated with constitutive ALL were integrated with DMCs associated with risk exposures to determine overlapping DMCs. Hypergeometric tests were used to assess the probability of relationships for any overlapping methylation change and when considering the directionality of methylation. Where exposures are hypothesised to increase ALL risk (i.e. maternal smoking, radiation and alcohol), we hypothesise observing the same directionality for exposure-related methylation and methylation in ALL. However, where exposures are hypothesised to be protective (i.e. maternal folate status, daycare attendance, reported cold) we assess directionally opposing methylation changes.

Results:

This sensitive CpG analysis reinforced earlier findings indicative of significant overlap between methylation changes observed in maternal plasma folate, radiation and alcohol exposure and ALL itself, and lack of associations for methylation associated with maternal folate supplementation and coffee consumption. Previously, sugary caffeinated drinks intake was observed to have significant overlapping gene methylation, however, overlaps for DMCs were not significant. For smoking related methylation, previous gene-level findings suggested significant overlap with ALL methylation, but not for concordance of directionality, whereas at CpG level neither overall nor concordant methylation was found to be significant. Where previously gene-level methylation associated with daycare attendance identified significant overlaps with ALL methylation, there were no DMCs found in common, suggesting that different gene regions have altered methylation in response to the exposure than in disease. Conversely, for reported colds, where overlapping gene methylation was previously found to be non-significant between exposure and ALL, the level of overlapping DMCs was found to be significant.

Conclusion:

Following our previous study of exposure-associated and ALL-associated methylation at gene-level, using a more sensitive CpG-level analysis, we corroborated earlier findings suggesting that DNA methylation associated with maternal radiation exposure, alcohol intake and plasma folate is also present in overt disease at a rate that is higher than expected by chance, therefore these exposures may contribute to disease aetiology through this mechanism. We suggest that our updated CpG-level analysis may be more robust due to the increased sensitivity to pinpoint the exact genomic position in which methylation has been altered, in comparison with our previous gene-level approach.

Targeted inhibition of Bcl-xL in H3K27M-altered diffuse midline glioma is a potent anti-tumour therapy

Ashley Vardon[1]

[1] University College London, Gower Street, London, WC1E 6BT

Background:

Paediatric-type Diffuse high-grade gliomas (PDHGGs) are aggressive brain tumours that treated palliatively with radiotherapy. Diffuse midline glioma (DMG) is a type of brain tumour that affects children and young adults. Specifically, a subtype which occurs in the pons, is particularly devastating, as it invades a part of the brainstem which is critical for functions such as breathing and heart rate. These tumours are particularly challenging to treat, as they are located in a critical area of the brain and are resistant to chemotherapy. Radiotherapy only provides a temporary relief to symptoms. Ultimately all children and young adults with this tumour type die. Therapy induced senescence is an emerging feature of residual disease following treatment with radiotherapy or chemotherapy. Senescence is a cellular phenotype following DNA damage, whereby cells through the senescence associated secretory phenotype (SASP) can promote tumour invasion and metastasis, but also through senescence bypass or escape cause tumour relapse. We hypothesised that following radiotherapy in PDHGG, the cells undergo senescence, and through the SASP or senescence escape, subsequently giving rise to tumour growth and relapse. We aim to understand whether using senolytic agents could be beneficial in combination with radiotherapy in these tumours.

Method:

We utilised clinically relevant doses of gamma-radiation, in primary human DIPG cell lines, reflecting both H3.3 and H3.1 histone mutated genotypes, and TP53 mutated and wild type cell lines. *In vitro* assays including, SA-BGal staining, EdU incorporation, growth assays, ELISA, immunofluorescence and RNA sequencing were utilised to interrogate the hypothesis, that radiation induces senescence in PDHGG cell lines. Next, we undertook a drug compound screen using CNS penetrant compound libraries, to understand if this senescence phenotype was a therapeutic vulnerability. In order to identify if Bcl-xL was critical to senescent cell survival we used a number of tool compounds and FDA approved drugs e.g. Navitoclax, we assessed cell viability using Cell-Titre Glo. Furthermore, to understand if combining radiation and senolytic could induce apoptosis, we used caspase 3/7 assays, and annexin V cell staining, to evaluate the mechanism of action. We investigated this hypothesis by combining with *in vivo* approaches using patient derived xenograft models of PDHGG to understand the impact of radiation-induced senescence *in vivo*. and the vulnerability of these cells to senolytic agents. Tumours were measured with bioluminescence, and growth was monitored over time. Mice were dosed with 50 mg/kg of Navitoclax and 6 fraction of 2Gy radiotherapy direct to the brain using a small animal radiation platform.

Results:

Senescence was confirmed using SA-B-Gal staining, lack of EdU incorporation and RNA-sequencing to evaluate the transcriptomic profile following radiation. We characterised the senescence associated secretome using ELISA of conditioned media and immunofluorescence of cells following radiation. Viable cells that survived radiation were then utilised to screen candidate senolytic drugs. We used a CNS penetrant 400 compound library, to evaluate novel senolytics. Only Bcl-xL inhibitors demonstrated reproducible senolytic activity in radiation treated PDHGG cell lines. Furthermore, we found in a xenograft model of PDHGG, we could prolong survival and reduce tumour burden when combining Navitoclax and radiotherapy.

Conclusion:

We found that radiation-induced senescence in PDHGGs creates a unique therapeutic opportunity that can be exploited using Navitoclax, a small molecule inhibitor ofBcl-2/Bcl-xL. We demonstrated that Navitoclax in synergy with radiation induces cell death in PDHGGs both *in vitro* and *in vivo*, resulting in a significant improvement in survival in preclinical models. Overall, our study sheds light on the role of senescence in PDHGGs and presents a promising therapeutic strategy for this deadly cancer. Our integrated approach that combines preclinical models, transcriptomic data, and immunohistochemical analyses can provide a framework for targeting senescent cells in PDHGGs.

Ketogenic diet as a metabolic vehicle for enhancing the therapeutic efficacy of mebendazole and devimistat in preclinical paediatric glioma

Purna Mukherjee[1]

[1] Boston College, 140 Commonwealth Avenue, Higgins Hall, Biology, Boston College, MA, USA

Background:

The alarming rise in incidence of glioblastoma (GBM) across all age groups over the last 21 years requires immediate action for management and prevention (1-3). Diffusely infiltrating paediatric high-grade gliomas (HGGs) through the brain and spinal cord are the leading cause of cancer death in children with no improvement in management in over 10 years (4-7). HGGs have been classified as anaplastic astrocytoma, diffuse intrinsic pontine glioma (DIPG), and glioblastoma multiforme (GBM) (8). Despite advances in treatment, survivors often suffer from life-long adverse effects of the toxic therapies (9). This study investigated the influence of nutritional ketosis on the therapeutic action of mebendazole (MBZ) and devimistat (CPI-613) against the highly invasive VMM3 glioblastoma cells in syngeneic juvenile p20-p25 mice; a preclinical model of paediatric HGG.

Method:

Young mice (p21-p25) of the VM/Dk (VM) were used for this study. VM-M3/luc labelled tumour cells were implanted orthotopically in the right cerebral cortex. Mice receiving the standard chow diet ad libitum for the duration of the study. Ketogenic diet were given ad-libitum so that the young mice can maintain the body weight for this short-term study. Mebendazole was administered to the mice mix thoroughly in the KD (100 mg/kg body weight) for 3 days consecutively/wk. CPI-613 was injected i.p. 0.5-1.0 mg/kg body weight once or twice in a week. The Ami HT system is used to record the bioluminescent signal from the labelled tumours as we previously described (10). Histopathological analysis was performed for the fixed tissues of brains and spinal cords. Liquid Chromatography Mass Spectrometry Analysis of Metabolomics were performed in MBZ treated VM-M3/luc cells. Western blot analysis was performed for Glutaminase-C expression in the drug treated brain tumour tissues. Tumour bioluminescence in-vitro, in-vivo, and ex-vivo data were analyzed using the one-way analysis of variance (ANOVA) followed by Mann Whitney test or by a student's t test. The survival studies were plotted on a Kaplan Meir curve using Graph Pad Prizm software and significance was determined using the log-rank test.

Results:

Cerebral implantation of the VM-M3 glioblastoma cells invaded throughout the brain and the spinal column like that seen commonly in children with HGG. The maximum therapeutic benefit of MBZ and CPI-613 on tumour invasion and mouse survival occurred only when the drugs were administered together with a ketogenic diet (KD). MBZ reduced VM-M3 tumour cell growth and invasion when evaluated under in-vitro and in-vivo conditions through inhibition of both the glutaminolysis and the glycolysis pathways. Moreover, administration of the drugs with the KD allowed lower dosing of the juvenile mice thus minimizing toxicity while improving overall survival.

Conclusion:

This preclinical study in juvenile mice highlights the potential importance of a diet/drug therapeutic strategy for managing childhood brain cancer. We also expect that this therapy could be effective for managing childhood HGG when used either alone or in combination with non-toxic aspects of standard of care. Our study will have a potential bench to bedside translation, especially for children with HGG.

Development of novel small-molecule drug combinations targeting high-risk *MYC*-driven medulloblastoma.

Louisa Taylor[1], Janice Law[1], Susie Cooper[1], Gemma Llargués Sistac[1], Laura Donovan[2], Alejandra Bruna[3], Louis Chesler[3], John Anderson[2], Rebecca M Hill[1] and Steve C Clifford

[1] Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne, UK
[2] UCL Institute of Child Health, London, UK
[3] Division of Clinical Studies, The Institute of Cancer Research, Sutton SM2 5NG, UK

Background:

Medulloblastoma represents the most frequent malignant childhood brain tumour. Under conventional treatment regimens, overall survival is approximately 70%. However, patients who exhibit amplification of the proto-oncogene MYC commonly present with rapidly progressive disease and define a subset of tumours that are almost universally fatal (<5% survival). Conventional up-front therapy, constructed based upon empirical clinical evidence rather than tumour biology, fails these patients and thus there exists strong rationale for the development of improved, targeted therapies against MYC-amplified disease. MYC is not directly targetable. Thus, the systematic development of combination therapies which target complementary MYC-dependencies offers clear potential to rationally re-design more effective chemotherapeutic strategies.

Method:

Semi-automated, high-throughput combination drug screening across two independent *MYC*-amplified cell-based models was utilised to assess drug-drug combinations across an 8x8 dose matrix for evidence of synergistic or additive effects (SynergyFinderPlus). Drug-drug combinations included ten small molecule MYC-dependency-targeting agents and five standard-of care therapeutics (cisplatin, lomustine, vincristine, etoposide, cyclophosphamide). Combinations were ranked according to degree of synergy/additivity and combination sensitivity score (CSS) and synergistic combinations validated in further cell-based systems. Soft agar colony formation assays, using two independent *MYC*-amplified isogenic cell lines with regulable shRNA MYC knockdown, were employed to assess the MYC-dependency of each drug-drug combination, alongside their impact on anchorage independent growth and cell death. Counter-screening against a panel of “normal” cell lines for cytotoxicity and cell viability allowed for initial assessment of adverse combination toxicities. Validation work included assessment of current up-front therapy combinations to benchmark novel combinations against standard-of-care.

Results:

105 drug-drug combinations were screened in total with an average Z’ Factor and co-efficient of variation (CV) of 0.71 ± 0.087 and 8.4% ± 2.6% respectively, indicative of a high-quality and reproducible screen. 17% of screened combinations were identified as synergistic, whilst 10% of screened combinations exhibited antagonistic effects. Synergistic drug-drug combinations included both anticipated and previously reported combinations (e.g. DNA damaging agent + DNA damage repair pathway inhibitor; AURORA kinase inhibitor + ATR inhibitor), as well as more novel drug-drug combinations (e.g. PHGDH inhibitor + platinum agent). Intriguingly, antagonistic drug-drug combinations included a number standard-of-care combinations, such as lomustine + cyclophosphamide, confirming the importance of rational, disease-biology based therapeutic design. All synergistic compound combinations were further validated *in vitro* to establish combination MYC-dependency and toxicity, the results of which informed a “Pre-Clinical Combination Strategy Board” which facilitated effective streamlining and prioritisation of drug-drug combinations (n = 3) for ongoing *in vivo* toxicity and efficacy studies.

Conclusion:

The systematic development of novel therapeutic strategies against MYC-amplified medulloblastoma represents an area of urgent unmet clinical need. We report here the establishment of an *in vitro* pre-clinical research pipeline to systematically and rigorously assess novel MYC-targeting therapy combinations for synergy, efficacy and toxicity. We anticipate ongoing testing in *in vivo* PDX and GEMM models of *MYC*-amplified disease will reveal effective MYC-dependent small-molecule combinations for early clinical development, providing much needed novel therapeutic options for this dismal prognosis disease group.

Genetic or pharmacological inactivation of CREBBP sensitises B-cell Acute Lymphoblastic Leukaemia to Ferroptotic Cell Death upon BCL2 Inhibition

Alicia Garcia-Gimenez, Jonathan E. Ditcham, Dhoyazan M.A. Azazi, Eshwar Meduri, Ryan Asby, Nathalie V. Sakakini, Cecile K. Lopez, Nisha Narayan, Shuchi Agrawal Singh, George Giotopoulos, Michael P. Murphy, Sarah J. Horton, Brian J.P. Huntly & Simon E. Richardson[1]

[1] Jeffrey Cheah Biomedical Centre, Puddicombe Way, Cambridge Biomedical Campus, CB2 0AW

Background:

B-cell acute lymphoblastic leukaemia (B-ALL) is an aggressive haematological malignancy of B lineage progenitors and is the commonest cancer in children. Whilst the majority of children can be cured with multi-agent chemotherapy, patients with high-risk genetic subtypes, certain age groups and those who relapse remain a clinical challenge, such that B-ALL remains a leading cause of death in childhood. There is therefore a need to better understand drivers of high-risk B-ALL and to develop novel therapeutic approaches targeting these challenging patient cohorts. Loss-of-function (LOF) mutations affecting *CREBBP* are recurrent second-hit mutation across multiple genetic subtypes of B-ALL and are associated with adverse features, including high-risk genetic subtypes and persistent measurable residual disease. In addition, they have been mechanistically associated with chemoresistance and are more frequently found in relapse.

Method:

In this study we sought to identify novel treatment options for *CREBBP*-mutated high-risk B-ALL. *CREBBP*-mutated isogenic human B-ALL cell lines were genome-engineered to provide a platform for synthetic lethal drug screening. We subjected the isogenic cell lines to a targeted drug screen, using a wide range of concentrations, focussed on clinically-actionable drugs in classes that have either been implicated or hypothesised to show differential sensitivity patterns in published models of B cell lymphoma and other *CREBBP*-mutated malignancies.

Results:

Unexpectedly, *CREBBP*-mutated cells were not differentially sensitive to traditional cytotoxic chemotherapy, and paradoxically showed a degree of sensitisation to the glucocorticoid dexamethasone, used in current ALL induction regimens. As anticipated, and validating our screen design, inhibitors of the *CREBBP* paralogue EP300 (the CREBBP/EP300-specific bromodomain inhibitor Inobrodib and the CREBBP/EP300 acetylase inhibitor A485) exhibited synthetic lethality, consistent with previous reports in B-cell lymphoma. The most potent hit was the BCL2 inhibitor Venetoclax, which we show acts through a non-canonical, but BCL2-dependent mechanism resulting in ferroptotic programmed cell death. *CREBBP*-mutated cell lines were transcriptionally and functionally characterised, revealing underlying differences in cell-cycle, metabolism and response to oxidative stress. Acquisition of resistance to Venetoclax further dysregulated these pathways and resulted in a transcriptionally-convergent state. Lastly, we demonstrate that small-molecule inhibition of CREBBP sensitises B-ALL cells, regardless of genotype, to Venetoclax-induced ferroptosis *in vitro* and *in vivo*, providing a potential novel drug combination for broader clinical translation in B-ALL.

Conclusions:

In summary, we have identified a number of actionable compounds that specifically target *CREBBP*-mutated high-risk B-ALL, demonstrate a novel mechanism-of-action for the BCL2 inhibitor Venetoclax in B-ALL and propose CREBBP-inhibitors and Venetoclax as a novel treatment combination for B-ALL more broadly.

VIVO Biobank – Uniting research into cancers in children and young people

Thomson LA[2], Smith A[2], Moppett J[3], Bacon CM[1], Moorman AV[1], Lloyd-Lewis B[4], Cragg E[1], Paizes E[1], Adetoro T[1] & Tweddle DA[1]

[1] Translational & Clinical Research Institute, Newcastle University
[2] University of York
[3] Royal Bristol Hospitals Trust
[4] University of Bristol

Background:

Celebrating 25 years of successful biobanking for Children and Young People with Cancer, the CCLG Tissue Bank is now joining with the Blood Cancer UK Childhood Leukaemia CellBank to form VIVO Biobank. A collaboration between Cancer Research UK and Blood Cancer UK, VIVO Biobank is the first national biomedical research resource dedicated to storing the samples and associated data of the full spectrum of cancers in children and young people.

Method:

VIVO Biobank contains all the samples from both existing banks, making a larger pool of tissues available from a single point of access. This allows streamlining of sample banking, sharing of expertise for sample handling and pan-cancer applications to be administered from a single access point to create a step-change in research. Solid tumours will continue to be stored at Newcastle University Biobank and liquid samples will continue to be processed and stored in UK Biocentre in Milton Keynes including liquid samples from solid tumours. Links are being established Genomics England and national datasets (NHS England, Public Health Scotland, SAIL Databank and the Northern Ireland Cancer Registry) to provide rich genomic and clinical data linked to the samples. Links with clinical trial units will be further strengthened. Pathways to increase banking rates for solid tumours and quality of leukaemia samples have been initiated, with a particular focus on improving banking in Teenagers and Young Adults (TYA). To help inform and steer our activities, we are forming a working group comprising parents, patients, carers, families and friends affected by childhood, teenage and young adult cancers.

Results:

VIVO Biobank currently holds over 204,000 samples (aliquots) from over 20,000 patients with many forms of cancer including acute lymphoblastic leukaemia, acute myeloid leukaemia, bone marrow failure disorders, CNS tumours, sarcomas, lymphomas, neuroblastomas and Wilms' tumours. Solid samples are stored at Newcastle University Biobank and liquid samples are stored at UK Biocentre. VIVO Biobank also houses a cord blood bank containing 700 HLA-typed samples. Since the Tissue Bank was founded in 1998, samples have been sent to 190 research projects and resulted in 166 publications. CellBank opened in 2007 and has provided samples to 96 projects resulting in 113 publications. The total number of research projects supported by the combined banks is 286, with an output of 280 publications in scientific journals. This research has had an impact on patient treatment.

The intrachromosomal amplification of chromosome 21 (iAMP21) is one of the most important prognostic markers for patients with Blineage acute lymphoblastic leukaemia. Research using CellBank samples proved that the clinical intervention of treating this group of patients more intensively was beneficial and reduced the rate of relapse from >75% to <25%. Research into miR-371~373 and miR-302/367 clusters showed that they are highly overexpressed in all MGCTs This is a disease specific change which led to the group being the first to demonstrate the utility of specific circulating microRNAs for diagnosis, disease monitoring and detection of relapse in GCTs. This has the potential to lead to earlier diagnosis of MGCTs without invasive, potentially risky physical biopsy.

Conclusions:

By merging our two existing biobanks –VIVO Biobank provides researchers with a single point of access for the widest collection of historic, current, and future samples available to support high quality research into children's and young people's cancer.

Identification of Distinct Prognostic Groups of Paediatric Brain Tumours Through Unsupervised Learning of Diffusion Weighted Imaging (DWI)

Timothy Mulvany[1], Daniel Griffiths-King[1], Lara Worthington[2,3], Richard Tunney[1], Theodoros N Arvanitis[2,4], Andrew Peet[2,4], John Apps[2,4], Jan Novak[1]

[1] Aston University, College of Health and Life Sciences, Birmingham
[2] Birmingham Children's Hospital, Department of Oncology, Birmingham
[3] University Hospital Birmingham NHS Foundation Trust, RRPPS, Birmingham
[4] University of Birmingham, Institute of Cancer & Genomics Sci, Birmingham

Background:

Predicting prognosis in paediatric brain tumours is a complex problem due the heterogeneity of patient health, tumour biology and treatment paths. Radiomics is the extraction of quantitative features from medical imaging that characterise an image. Increased availability of medical imaging and long-term survival data has enabled the use of radiomics with machine learning for prognostic prediction. This study expands on current literature, evaluating the prognostic utility of DWI via unsupervised learning, and the combination of DWI with patient demographics.

Method:

This study utilised retrospective clinical data from 84 paediatric brain tumour patients with long term-survival information made available via the Children's Cancer & Leukaemia Group's long term functional imaging study (established 2004). 24 first order radiomic features of tumour regions were extracted from Apparent diffusion coefficient (ADC) maps generated using DWI data acquired at 1.5T across four scanners located at Birmingham Children's Hospital using b-values 0 and 1000 s/mm2. ADC is a putative marker of cellularity which has established links with progression-free survival.

Balanced Iterative Reducing and Clustering using Hierarchies (BIRCH) was used to identify two underlying clusters of patients within the dataset, based upon the quantitative description of their DWI Prognostic significance of clusters was assessed using Hazard Ratios (Cox Proportional Hazards Regression). Input feature sets were dimensionally reduced prior to training (Principal Component Analysis). This was repeated when testing the prognostic utility of including patient age and sex.

Results:

BIRCH successfully identified two clusters of patients with significant prognostic value ($p<0.05$) for both feature sets. Using ADC features alone distinguished two clusters of patients with significantly different risk, obtaining a hazard ratio of 4.71($p=0.0383$). With the inclusion of patient demographics, the resulting hazard ratio was significantly increased to 9.83 ($p=0.0262$). Kaplan Meier curves show the long-term survival for each cluster of patients.

Conclusion:

Despite a complex and noisy prediction space, unsupervised clustering of simple first-order ADC radiomic features has established the existence of two prognostically distinct patient groups. The inclusion of demographic information alongside radiomic features enhanced prognostic prediction for paediatric patients improving risk differentiation. Further validation utilising larger datasets is essential to evaluate the generalisability of these findings. Understanding the histopathological characteristics and diagnosis of patients within these clusters is vital to determine any underlying biological mechanisms that may assist clinical interpretation of these risk profiles.

Improving the journey of children with lymphadenopathy: a collaborative approach between a Tertiary Children's Cancer centre and Local Integrated Care Service and Board

Benjamin Miguras[1], David Hobin[1], Jake Matthews[1]

[1] Birmingham Children's Hospital

Background:

Children with enlarged lymph nodes are a common presentation to healthcare, especially primary care. Underlying malignancy is rarely the cause. They are a significant cause of stress and anxiety to patients, carers and clinicians. Despite a number of published guidelines, our anecdotal experience was a lack of clarity on the appropriate referral pathway for managing these patients in our local setting.

The establishment of the ICS and ICB structure in the West Midlands has facilitated more direct engagement between the tertiary children's cancer service and primary care. We used this new relationship to explore how the management of lymphadenopathy in children could be improved. Our aim for this project was to investigate the current management of lymphadenopathy in the primary care setting in Birmingham through collaboration with the Birmingham Solihull Integrated Care Board (BSol ICB), identify possible knowledge gaps, develop educational opportunities and produce a standardised algorithmic approach to determine the most appropriate pathway for patients.

Method:

A Google Forms survey was distributed to primary care physicians via the ICS network. The survey contained clinical vignettes and generic questions to understand current practice and approach to managing lymphadenopathy. The survey aimed to understand awareness of guidance and resources.

Results:

There were 31 responses, with 22 from the BSol group. Based on the vignettes, there was a clear awareness of the 'red flag' features of lymphadenopathy. Clinicians generally reported feeling 'comfortable' managing lymphadenopathy. The majority of clinicians would prioritise a face-to-face review. A small proportion would seek senior support or review guidelines. There was a limited awareness of the 'Paediatric Top 20' document developed by Birmingham Children's Hospital specifically to support the management of common childhood conditions. For non-progressive lymphadenopathy, nearly 75% would request blood and/or imaging tests despite half of respondents identifying no features of malignancy. In the cases suggesting infective or reactive lymphadenopathy, a course of antibiotics was chosen by 4 respondents. Responses to the case suggesting lymphoma indicate that there is good awareness of malignant lymph node characteristics. A chest X-ray to identify mediastinal masses was suggested by 2/22 clinicians. A quarter of clinicians referred directly to paediatric oncology, with only two requesting telephone conversations. The responses to the survey were in contrast to the review of urgent 2WW referrals received in a similar time period. There were 24 referrals, eight accepted and sixteen withdrawn. Of those withdrawn, 13 were discussed with an oncologist and management plan agreed and de-escalated. From the accepted referrals, 3 had investigations including USS, cross-sectional imaging and biopsy. The remaining 5 were reactive or regressive lymphadenopathy and discharged. None of the children investigated had a malignant diagnosis causing lymphadenopathy.

Conclusion:

In conclusion, the survey confirmed that clinicians are aware of 'red flag' features of lymphadenopathy but do not follow standardised management and are unsure about the best referral pathway within the region. This has resulted in the provision of a primary-care focused education event led and delivered by the Tertiary Children's Cancer team and an algorithm to support management of paediatric lymphadenopathy.

CNS 2004 10 Imaging of Tumours Study: Past, Present and Future

John Apps[1], Theodoros Arvanitis[1], Lesley MacPherson[2], Darren Hargrave[3], Richard Grundy[4], Andrew Peet[1]

[1] University of Birmingham
[2] Birmingham Children's Hospital
[3] University College London, Great Ormond Street Hospital
[4] University of Nottingham

Background:

On behalf of the CCLG Functional Imaging of Tumours Group and Imaging of tumours Study Management Group.
The CCLG CNS 2004 10 Imaging of Tumours study is a world leading study that has driven the development of advanced imaging techniques, radiomics and clinical decision support tools in the UK and worldwide. We present an overview of the achievements of this study, current status and plans for the future.

Method:

CNS 2004 10 is a single arm observational study opened in October 2004 as the MRS of Brain Tumours Study. It subsequently changed its name to the Functional Imaging of Tumours Study in 2012 and in 2023 to the Imaging of Tumours Study. A CRN Portfolio study open at 11 UK centres it has recruited over 1650 patients and collects imaging, including advanced MRI, through a web accessible database with a custom developed pseudonymisation tool. Consent includes collection of clinical data, including indefinite follow up and correlation with biological samples and data. The current aims of the study are:

1) To develop imaging methods for the diagnosis, management and understanding of tumours in the foetus, children and young people.

2) To integrate analysis of imaging data, with clinical data and biological data for the improved understanding and characterisation and to support the diagnosis, treatment and monitoring of children with tumours.

Patient involvement and engagement has been an important part throughout the study and will continue into the future.

Results:

Over 120 papers, reviews, book chapters and guidelines have been published through this study, including 127 original research papers and winner of best basic science paper in Paediatric Radiology. Highlights include studies into novel imaging techniques, radiomics, improving diagnosis, and predicting outcomes within and across tumour types, as well as qualitative studies as to the importance of imaging to patients. An artificial intelligence based clinical decision support tool is being developed to support radiologists in diagnosing tumours. Work through this project has directly fed into international imaging guidance for children with brain tumours. The study has supported the training of over 20 PhD students and numerous post-doctoral research fellows and clinical fellows many of whom have gone on to become lead investigators/independent researchers.

Conclusion:

The CNS 2004 10 Imaging of Tumour study provides a opportunity to continue to drive forward research into Children's Tumours. Meetings in 2022 and 2023 with stakeholders, including clinicians, scientist, patient's and patient groups, have supported its continuing development and the strength and enthusiasm of the diverse skilled community behind the project. Substantial amendments are in process to update study governance, facilitate easier data sharing and integration with synergistic projects and endeavours, and facilitate add on studies addressing relevant clinical and scientific questions and challenges.

Differential Expression of miRNAs in Adamantinomatous Craniopharynngioma Reveals Dysregulation of Pathogenic Pathways

John Apps[1], Juan Pedro Martinez-Barbera[2]

[1] University of Birmingham
[2] University College London

Background:

Adamantinomatous Craniopharyngioma (ACPs) are benign pituitary tumours that can result in significant morbidity and premature mortality. ACPs harbour mutations in CTNNB1 and are driven by the activation of the WNT/beta-catenin pathway. Through work by the Childhood Craniopharyngioma Research Consortium, funded by Children with Cancer UK, and others, novel therapies for Adamantinomatous Craniopharyngioma (ACP) identified through gene expression profiling are now being tested in clinical trials. MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression of target mRNAs and can control whole gene networks. We sought to explore the expression of miRNAS in adamantinomatous craniopharyngioma (ACP) in a cohort of samples previously subjected to RNA-Seq analysis (Apps et al, Acta Neuropathologica, 2018, May;135(5):757-777).

Method:

Total RNA from ACP samples (n=18), non-functioning pituitary adenomas (n=3) and normal foetal pituitaries (n=3) underwent miRNA sequencing using the Qiagen miRNA library prep kit on a NextSeq 500 to a depth of 16 million reads. Differential expression was performed using DESeq2 and functional analysis with mirPath v.3. Expression of miRNAs was correlated with previously published mRNA expression.

Results:

We found that 210 miRNA were upregulated and 275 down regulated in ACP compared with controls (adjusted p-value < 0.1). MIR-205-5p was the most upregulated miRNA (619 fold) and its expression correlated with genes expressed within the tumour epithelium (e.g. TP63). miR-375 an inhibitor of the WNT pathway was the most down regulated miRNA (361 fold). KEGG Pathway analysis identified Glycosphingolipid synthesis as the most enriched pathway targeted by upregulated miRNAs. Pathways that were enriched by down regulated miRNAs included: ECM-receptor interaction, fatty acid biosynthesis, Hippo, TGF-beta, WNT, and ErbB pathways. Down regulation of miR-132 has previously been suggested as a marker of aggressiveness in ACP, and was 16 fold down regulated (adjusted p-value< 0.001) in this cohort and expression was inversely correlated with genes relating to epithelial development.

Conclusion:

This data confirms previous studies indicating that miRNA expression is altered in ACP. In silico analysis suggest that the dysregulation of miRNA affects the expression of genes involved in pathogenic pathways in ACP.

Exploring the potential role of environmentally-associated DNA methylation to contribute to risk of different subtypes of childhood acute lymphoblastic leukaemia

Jessica Saville[1], Jill McKay[1], Lisa Russell[2], Kay Padget[1]

[1] Faculty of Health and Life Sciences, Department of Applied Sciences, Northumbria University
[2] Biosciences Institute, Newcastle University Centre for Cancer, Faculty of Medical Science, Newcastle University

Background:

Acute lymphoblastic leukaemia (ALL) is a heterogenous disease with unclear aetiology. Various genetic aberrations have been retrospectively detected at birth and are suggested to be initiating events in disease development. ALL can be categorised into cytogenetic subtypes based on the alterations they possess. However, further factors, such as epigenetic modifications, are required for disease progression. Previously we provided evidence to suggest that DNA methylation may be a mediating mechanism through which some environmental factors may contribute to ALL manifestation. Due to the differing genetic profiles of the subtypes, it is plausible that different exposures may pose differing levels of risk for each subtype. Here we have employed our previously established, meet-in-the-middle approach, to perform CpG-based analysis to investigate DNA methylation as a mediating mechanism between potential risk exposures and specific ALL-subtypes.

Method:

Differentially methylated CpGs (DMC's) associated with ALL environmental risk factors were identified using previously published data. We then selected data measuring DNA methylation in ALL, where analysis of 10 cytogenetic subtypes were considered. DMCs associated with cytogenetic subtypes were integrated with DMCs associated with risk exposures. Hypergeometric tests were used to assess the probability of relationships between exposure-associated and ALL-associated methylation for any overlapping methylation change, and when considering the directionality of methylation. Where exposures are hypothesised to increase risk (i.e. maternal smoking, radiation and alcohol), we hypothesise observing the same directionality for exposure related methylation and methylation in ALL. However, where exposures are hypothesised to be protective (i.e. maternal folate status, daycare attendance, reported cold) we assess opposing methylation changes.

Results:

Significant overlapping methylation differed between cytogenetic subtypes for different exposures. When DMCs for exposures associated with increased risk were analysed by subtype significant CpG overlaps in the same direction are observed for radiation and MLL, for alcohol intake with T-ALL and ETV6-RUNX1 and for smoking throughout pregnancy with MLL and undefined subtypes. For protective exposures analysed by subtype, significant overlaps in opposing directions are observed for methylation associated with reported colds and the MLL subtype. For maternal plasma folate, overlapping methylation changes in opposing directions are observed for 8/10 subtypes.

Conclusion:

Environmental exposures may influence risk of ALL in a subtype-specific manner via exposure-associate methylation. Whilst the potential influence of maternal folate exposure during pregnancy on methylation patterns that may contribute to ALL appears to be fairly consistent across most subtypes, the epigenetic effect of other exposures may be more likely to contribute to the development of specific subtypes. This analysis is therefore useful in understanding which risk factors may contribute to specific subtypes of leukaemia and those which more generally influence ALL risk. Such knowledge may be useful to influence public health policy to aid and tailor prevention strategies.

What is the evidence base for long term use of methylphenidate in the childhood Acquired Brain Injury population?: A Systematic Review

Thomas Harrison[1], Pattramon Pornsukjantra[1], Alexander Hagan[1], Sarah Verity[1,2]

[1] Department of Paediatric Health Psychology, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK, NE1 4LP
[2] Newcastle University Centre for Cancer, Newcastle upon Tyne, UK, NE1 7RU

Background:

Survivors of childhood brain tumour often report chronic and debilitating neurocognitive consequences of disease and treatment. Whilst research has explored the potential utility of methylphenidate in childhood survivors of Acquired Brain Injury (ABI) including brain tumour, few studies have attempted to substantiate its utility beyond short-term use. The present systematic review aims to assess the benefit of methylphenidate on long-term (>6 months) neuropsychological outcomes within a mixed childhood ABI sample.

Method:

Database searches were conducted in MEDLINE, PsycINFO, EMBASE, and Cochrane Library from their inception to March 2023. Studies containing a neurocognitive, psychosocial, or quality of life outcome measure were included. A purpose-developed evaluation tool was used to assess the quality of the evidence base.

Results:

Six of the 1925 identified articles were included within this review. Results drew upon four clinical populations (N = 433); brain tumour (n = 113), acute lymphoblastic leukaemia (n = 89), epilepsy (n = 154) and other EEG abnormalities (n = 77). Study duration ranged between 6 - 12 months. Initial analyses reported benefits of long-term use of methylphenidate on attentional functioning, social skills, and health-related quality of life. Side effects of methylphenidate in long-term use were reported to be mild and temporary. Studies in this population continuing beyond 12 months were not identified by this review.

Conclusion:

Methylphenidate demonstrates potential benefit in the medium term for neurocognitive late effects reported by childhood survivors of ABI including survivors of brain tumour. There is a clinical need to substantiate any potential benefit of methylphenidate beyond the medium term.

Testicular germ cell tumour cells release microna-containing extracellular vesicles resulting in promalignant changes in cells of the tumour microenvironment

Luz Alonso-Crisostomo[1], Jennifer Trendell[1], Marta Ferraresso[1], Shivani Bailey[1], Dawn Ward[1], Carlos A. P. Bastos[2], Ravin Jugdaohsingh[2], Nuno J. Faria[2], Anton J. Enright[1], Cinzia G. Scarpini[1]*, Nicholas Coleman[1,3]*, Matthew J. Murray[1,4]*

[1] Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QP, UK.
[2] Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge, CB3 0ES, UK
[3] Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK.
[4] Department of Paediatric Haematology and Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK.
* Joint senior authors

Corresponding author: Professor Matthew Murray, Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QP, UK; Telephone 0044 (0)1223 765066; email mjm16@cam.ac.uk. ORCID identifier: 0000-0002-4480-1147.

Background:

MicroRNAs (miRNAs/miR-) are short, non-protein coding RNAs that are dysregulated in malignant germ cell tumours (GCTs), with universal over-expression of miR-371~373 and miR-302/367 clusters regardless of patient age, tumour site, or subtype (seminoma/yolk-sac-tumour/embryonal carcinoma). These miRNAs are released into the bloodstream, presumed via extracellular vesicles (EVs), and represent promising biomarkers. Here, we comprehensively examined the role of EVs, and their miRNA cargo, on (fibroblast/endothelial/macrophage) cells representative of the testicular GCT (TGCT) tumour microenvironment (TME).

Method:

Small RNA next generation sequencing was performed on 34 samples, comprising representative malignant GCT cell lines/EVs and controls [testis fibroblast (Hs1.Tes) cell-line/EVs and testis/ovary samples]. TME cells received TGCT-derived EV treatment, miRNA quantification by qRT-PCR, and a miRNA overexpression system (miR-371a-OE) to perform functional assays and assess mRNA changes.

Results:

TGCT cells secreted EVs into culture media. MiR-371~373 and miR-302/367 cluster miRNAs were over-expressed in all TGCT cells/subtypes compared with control cells and were highly abundant in TGCT-derived EVs, with miR-371a-3p/miR-371a-5p the most abundant compared with normal EVs. Fluorescent labelling demonstrated TGCT-derived EVs were internalised by all TME cells. TME (fibroblast/endothelial) cell treatment with EVs derived from different TGCT subtypes resulted in increased miR-371~373 and miR-302/367 miRNA levels, and other generic (e.g., miR-205-5p/miR-148-3p), and subtype-specific (seminoma, e.g., miR-203a-3p; yolk-sac-tumour, e.g., miR-375-3p) miRNAs. MiR-371a-OE in TME cells resulted in increased collagen contraction (fibroblasts) and angiogenesis (endothelial cells), associated with dysregulation of mRNAs and relevant cellular pathways.

Conclusions:

TGCT cells communicate with non-tumour stromal TME cells through release of EVs enriched in oncogenic miRNAs, likely contributing to tumour progression.

Combined epigenetic and retinoic acid therapy in the treatment of paediatric sarcoma models

Carmen Tse[1]

[1] University of Southampton, Institute of Developmental Sciences, 216 Tremona Rd, Southampton, SO16 6HW

Background:

Rhabdomyosarcoma (RMS) is a paediatric sarcoma that originates from muscle precursor cells as a result of impaired myogenic differentiation. Patients with advanced disease show a 5-year survival of 20%, highlighting a need for novel therapies to improve outcome and survival. Differentiation therapy involves the use of agents that induce differentiation in order to alter the phenotype of cancer from malignant to benign, resulting in terminal differentiation or programmed cell death. Histone methyltransferase, Enhancer of Zeste Homolog 2 (EZH2) is involved in the suppression of skeletal muscle differentiation and was found to be aberrantly regulated in RMS primary tumours and cell lines. EZH2 inhibitors (EZH2i) have shown an anti-proliferative effect against RMS cells through the induction of myogenic differentiation. Retinoic acid, ATRA is a differentiation agent that has been successfully used in the treatment of acute promyelocytic leukaemia and neuroblastoma. However, the use of ATRA in RMS show varying levels of success. The aim was this study was to investigate if the use of a combination of differentiation agents could lead to better RMS therapy.

Method:

We used *in vitro* 2D and 3D RMS models to explore the efficacy of EZH2i, GSK343 and ATRA combination treatment using proliferation assays, western blotting, immunohistochemistry, ChIP-seq and RNA-seq.

Results:

We found that the combination treatment was more effective at reducing cell proliferation in the RMS cell lines than single agent treatment. In PAX3-FOXO1 positive RMS cells this is due to an RA-driven induction of the interferon pathway resulting in apoptosis. In fusion negative RMS, combination therapy led to an EZH2i-driven upregulation of myogenic signalling resulting in differentiation.

Conclusion:

These results provide an insight into the mechanism of EZH2i and retinoic acid therapy as single agent and in combination. The reduction of EZH2 activity in addition to the induction of RA signalling could represent a novel adjuvant strategy to potentially treat both subtypes of RMS.

Development of an allogeneic V-delta-1 gamma delta T chimeric antigen receptor cell product for childhood solid cancers

John Anderson[1], Gabrielle Ferry[1], Charles Agbuduwe[1], Dan Fowler[1], Kerry Chester[1], Marta Barisa[1]

[1] UCL Great Ormond Street Institute of Child Health, 30 Guildford Street, London, WC1N 1EH

Background:

Chimeric antigen receptor gene modified conventional T cells (CAR-T cells) have shown preliminary encouraging activity in neuroblastoma patients but the cost and complexity of manufacture of personalised autologous products is a potential roadblock slowing clinical translation. Gamma delta T lymphocytes represent on average 1-5% of circulating T cells, exist in two main subtypes Vδ2 and Vδ1, possess innate anti-cancer properties, and do not interact with MHC hence do not cause graft versus host disease in the allogeneic setting. The natural tissue tropism of the Vδ1 subset mark them out as an attractive subset for solid tumour adoptive immunotherapy.

Method:

Vδ1 and Vδ2 T cells were expanded in the presence of IL-15 from adult peripheral blood or cord blood using stimulation with anti-CD3 antibodies following depletion of alpha beta T cells and CD56+ cells. Expanding γδT cells were transduced with lentiviral vectors encoding anti-B7H3 chimeric antigen receptors and a range of cytokine signal modules and evaluated for IL-15 independent growth, cytotoxicity and cytokine response in coculture with neuroblastoma cell targets.

Results:

A pure population of gamma delta T cells of predominantly Vδ1 subtype was reproducibly expanded from cryopreserved apheresate of 6 healthy donors or 3 cord blood products with expansions of 400-5,000 fold. With transductions using standard CAR-T lentivectors expressing a novel B7H3 targeting construct on days 2-4 following stimulation, between 40-80% CAR-positive cells were attained at harvest on days 14-18. Following IL-15 withdrawal Vδ1 CAR-T cells showed drastic loss in viability and effector function despite CAR engagement indicating IL-15 signalling dependency. Construct modifications designed to overcome IL-15 addiction included cytokine receptor endodomains, co-expressed activated STAT5 proteins and co-expressed IL-15. Of these, the combination of co-expressed IL-15 and anti-B7H3 CAR was most successful, leading to sustained CAR-T activity in the presence of B7H3 expressing neuroblastoma target cells in the absence of exogenous IL-15. The expanded Vδ1-CAR-T cells had no reactivity against allogeneic healthy cells.

Conclusion:

We have developed a protocol for reproducible expansion of a tumour-reactive CAR-T product which is boosted by but not totally dependent on the target antigen for tumour specific killing, and that naturally lacks an alloreactive T cell receptor. We have identified an engineering strategy to render cells independent of exogenous cytokine support. The broad expression of B7H3 target antigen in childhood solid cancers renders Vδ1-CAR-T an attractive product for evaluation in a basket trial of off the shelf cell therapy in patients with relapsed disease expressing this target antigen.

VIVO BIOBANK – Supporting Cancer Research to Improve Patient Treatment

Thomson, L.A[2], Adetoro, T[1], Smith, A[2], Moppett, J[3], Bacon, C.M[1], Moorman, A.V[1], Lloyd-Lewis, B[4], Cragg, E[1,] Paizes, E[1] & Tweddle, D. A[1]

[1] Translational & Clinical Research Institute, Newcastle University, Newcastle upon Tyne
[2] University of York, York
[3] Royal Bristol Hospitals Trust, Bristol
[4] University of Bristol, Bristol

Background:

Celebrating 25 years of successful biobanking for Children and Young People (CYP) with Cancer, the CCLG Tissue Bank has joined with the Blood Cancer UK Childhood Leukaemia CellBank to form VIVO Biobank. A collaboration between Cancer Research UK and Blood Cancer UK, VIVO Biobank is the first national biomedical research resource dedicated to storing the samples and associated data of the full spectrum of cancers in children and young people.

Method:

Samples from children and young people with all types of cancer are available from VIVO Biobank for ethically-approved, peer-reviewed research. VIVO Biobank is open to both UK and International researchers.

Results:

Research using samples from patients with leukaemia and those with solid tumours has had major impacts on the treatment of children and young people with cancer as illustrated in our case studies.

Case study 1

A genetic rearrangement which brings together two important genes, the immunoglobulin gene and MYC, is typical of Burkitt lymphoma. However, it is also seen in other blood cancers including in a disease which presents as acute lymphoblastic leukaemia (ALL). Until recently doctors have not known whether these patients have ALL with the “Burkitt lymphoma” rearrangement, or Burkitt lymphoma which just “looks like” ALL. Over the last five years, an international collaboration, including samples from CellBank, has shown these patients have an aggressive ALL with a very poor outcome. Results from this research has influenced clinical decision making and clinical trial development and the pan-European trial ALL Together 01 altered its inclusion criteria to include these patients. This will allow better information to be collected for these patients thereby improving their therapy and eventually outcome.

Bomken,S., et al. (2023). Haematologica, 108(3), 717-731 https://doi.org/10.3324/haematol.2021.280557

Case study 2

Investigation into ALK genetic modifications in high-risk neuroblastoma patients revealed that particular alterations, such as clonal mutations and amplifications, are associated with worse survival outcomes. Consequently, it has been proposed that patients exhibiting these alterations should be given priority treatment with ALK inhibitors. This approach is currently being applied in the High Risk Neuroblastoma Study 2 (HR-NBL2) trial. Furthermore, additional preclinical studies aimed at understanding the treatment of ALK-aberrant high-risk neuroblastoma have demonstrated that specific ALK inhibitors exhibit improved effectiveness.

Bellini et al. (2021), Journal of Clinical Oncology, 39(30), 3377–3390 https://doi: 10.1200/JCO.21.00086
Tucker et al. (2023), Clin. Cancer Res. 29(7):1317-1331. https://doi: 10.1158/1078-0432.CCR-22-2274

Conclusion:

VIVO Biobank has been providing samples to research via its constituent banks for 25 years. Bringing together samples from all CYP cancer types will facilitate pan-cancer research. VIVO Biobank provides researchers with a single point of access for the widest collection of historic, current, and future samples available to support high quality research into children’s and young people’s cancer

Psychosocial interventions to improve wellbeing in teenage and young adult (TYA) post-treatment survivors of childhood cancer: a systematic review and meta-analysis

Nicola O’Donnell[1], Leila Ellis[2], Bob Phillips[1], Jess Morgan[1], Victoria Willard[3]

[1] University of York
[2] University of Bristol
[3] St Jude Children’s Research Hospital

Background:

It has been well documented that once in remission from cancer, individuals and their families can be left ‘in limbo’ (Lopez et al., 2014). This description captures the survivorship journey towards normality and a life without active treatment, but with an impact on wellbeing, the potential additions of fear of recurrence and social difficulties when reintegrating into ‘normal life’ (Wakefield et al., 2010). In an attempt to reduce such difficulties, psychosocial interventions are increasingly used in clinical practice. Despite this, little is known about the feasibility and efficacy of these, particularly for childhood cancer survivors who are now teenagers and young adults (TYA) (Campo et al., 2017; van Dijk-Lokkart et al., 2016). TYA in cancer settings are classed as a unique group, situated in the middle of healthcare systems aimed at either children or adults (James Lind Alliance, 2018). For this reason, the psychological support needs of survivors of childhood cancer has been named as a JLA top 10 priority (James Lind Alliance, 2022). The psychosocial impact of childhood cancer on this group can be vast, as many experience interrupted development, impacting their cognitive and social outcomes (Patterson et al., 2015). Therefore, tailored psychosocial care and interventions must be offered, flexibly responding to the needs of individuals at this life stage (D’Agostino et al., 2011).

Method:

This systematic review and meta-analysis aimed to explore psychosocial interventions designed for Teenage and Young Adult (TYA) survivors of childhood cancer, including:
1) What types of psychosocial interventions exist for TYA survivors of childhood cancer?
2) Is there a type of psychosocial intervention that provides higher efficacy in improving survivors’ mental wellbeing?
3) Do psychosocial interventions positively influence the wellbeing and psychological health of TYA survivors’ and are there any possible negative impacts or ‘adverse events’?

A protocol was produced and registered prospectively on PROSPERO (CRD42023422933). This review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The literature was searched extensively and systematically for studies that evaluated any intervention delivered to TYA aged 13-39 post-treatment survivors of any type of cancer. This age range incorporates UK and USA definitions of ‘TYA’ as per National Cancer Institute, Cancer Research UK, and James Lind Alliance guidance. MEDLINE ALL, PsycINFO, Scopus, Cochrane Library, CINAHL (EBSCO), British Nursing Database, PsycARTICLES, and EMBASE databases were searched to identify studies meeting inclusion criteria. Furthermore, PROSPERO and clinical trial registries were used to scope any unpublished or ongoing reviews and studies on a similar topic. Forward and backward citation searches were also included.

Results:

Analysis of results is ongoing at time of abstract submission with initial findings expected to be available by September 2023 for release at the Children with Cancer UK Childhood Cancer Conference.

Conclusion:

This study closely aligns with the Children with Cancer UK 2022-2027 research priority aiming to improve development of more effective treatments recognising the short- and long-term psychosocial wellbeing and mental health effects of childhood cancer. This work has been conducted through a multidisciplinary collaboration between University of York, University of Bristol and St. Jude Children’s Research Hospital.

A qualitative investigation into the psychosocial needs of teenagers and young adults who have had Retinoblastoma

Nicola O'Donnell[1], Bob Phillips[1], Jess Morgan[1], Debra Howell[1]

[1] Epidemiology and Cancer Statistics Group, University of York, York, YO105DD

Background:

Retinoblastoma is a rare childhood cancer that is diagnosed in approximately 40-50 UK children a year, with 45% due to hereditary factors (Jenkinson, 2015; Hülsenbeck et al., 2021). Although highly curable, Retinoblastoma can have a huge impact on the psychological wellbeing of individuals long after their treatment has ended (van Dijk et al., 2009). For many their vision is impaired, and they may experience eye loss or facial changes (Sethi et al., 2014; Temming et al., 2016). For others, there will be lifelong anxiety about the development of second cancers and the possibility of future children developing Retinoblastoma too (Hill et al., 2018). Existing research has highlighted the need for psychosocial support in this population, yet we know that the nature of this support is under-researched and largely unavailable (van Dijk et al., 2009; Ford et al., 2015; Belson et al., 2020; Gregersen et al., 2021). This study is the first of three projects that aims to understand the psychosocial needs of young people living beyond Retinoblastoma. It will provide rich information about an individual's experiences that will inform future psychoeducation interventions. This will be of significant benefit as there is currently no routine psychological support offered to young people as they transition from childhood and begin to navigate the vast impact of life beyond Retinoblastoma.

Method:

A qualitative study was conducted: focus groups with 16 teenagers (13-19 years) and individual interviews with 16 young adults (20-29 years) (TYA) with a history of Retinoblastoma. For both participant interviews and focus groups, a wide inclusion criteria was set. This was to encourage individuals with diverse experiences to take part, this included;

any form of Retinoblastoma (heritable or non-heritable), bilateral or unilateral, any age of diagnosis, and any treatment regime. The study aimed to explore living beyond Retinoblastoma and challenges that may be faced as a result. A narrative approach explored life-stories of individuals and aimed to gain clear understanding of transition to adulthood. It also sought views on challenges experienced and current psychosocial support they access or felt could be beneficial.

Results:

Data was collected between June 2022 – January 2023 and was analysed using Braun and Clarke's reflexive thematic analysis (Braun and Clarke, 2021). Three themes and eight subthemes were identified:

1. Childhood 'the legacy of trauma' (a) family experiences and survivor guilt, b) memories from treatment, c) the long-lasting impact on personality)

2. Adolescence 'when you're a teenager, you feel like everything is the end of the world' (a) psychological impact, b) identity, c) 'normal' for me)

3. Adulthood 'it's not meant to be for life, but it carries on' (a) acceptance, b) doing 'the work').

TYA discussed increased anxiety, both socially and in terms of their health. This included concerns about second cancers, and about passing on Retinoblastoma genes to future children. For many, they internalised Retinoblastoma and the domination of this on their identity. There was also a focus on a lack of targeted psychological support, and the need for education and information about the long-term impact of childhood cancer.

Conclusion:

TYA who have had Retinoblastoma appear to be at increased risk of anxiety and identity-related distress. This is particularly apparent for those with the hereditary variant, as well as those who were treated with enucleation and therefore have a visible difference that others can detect. There is also a high need for targeted Rb psychosocial support, which is supported by existing evidence and supports our plan to develop a novel psychoeducation intervention for this population.

Oncohistones promote cancer plasticity

Alan Jiao[1]

[1] Ludwig Institute for Cancer Research, Oxford University, Old Road Campus Research Building,

Oxford, OX37DQ

Background:

Phenotypic plasticity is an increasingly appreciated hallmark of cancer cells. Pediatric gliomas known as DIPGs (diffuse intrinsic pontine gliomas) are driven by H3K27M oncohistone mutations, which act as potent inhibitors of Polycomb Repressive Complex 2 (PRC2). How these mutations promote tumorigenesis is not fully understood.

Method:

We applied serum-induced differentiation or prolonged chemo drug treatments to reveal phenotypic plasticity, and use CRISPR-gene editing to elucidate the genetic factors driving plasticity.

Results:

Following serum-induced differentiation, a subpopulation of differentiation-resistant cells can emerge, but only in the presence of H3K27M and the proneural transcription factor (TF) ASCL1. These cells resist the induction of mesenchymal gene signatures, upregulate ASCL1 and SOX TF family activity, and exhibit a unique H3K27me3 profile – suggesting H3K27M-expressing cells can adopt one of two epigenetic states under differentiating conditions. As further evidence for H3K27M-dependent plasticity, we show H3K27M promotes tolerance to diverse chemo drugs. Drug tolerant persisters can exhibit features of both differentiation-induced states (e.g. upregulated SOX family targets and upregulated mesenchymal signatures).

Conclusion:

We propose H3K27M facilitates access to multiple transcriptional states, endowing mutant cells with increased phenotypic plasticity that may be central to gliomagenesis and therapeutic resistance.

High-resolution deconvolution signatures for cross-species investigation of the medulloblastoma tumour immune microenvironment (TIME)

Dean Thompson[1], Louisa Taylor[1], Rebecca Hill[1], Steven C. Clifford[1], Laura Donovan[2], John Anderson[2]

[1] Wolfson Childhood Cancer Research Centre, Newcastle University
[2] University College London

Background:

Amplification and overexpression of the MYC oncogene is common in Group 3 medulloblastoma (MB), presenting in ~20% of cases. It is almost universally fatal, and alternative therapies are urgently needed for these patients. High MYC expression is recognised to play an immunosuppressive role in other cancers, and in silico characterisation of the MB tumour immune microenvironment (TIME) has confirmed immune infiltration to be low. Therapeutic modulation of MYC may be hypothesised to increase immune infiltration in MYCMB Group3 tumours, rendering them susceptible to immunotherapies such as CAR-T. Currently, TIME characterisation within MB is restricted to low-resolution in human tumours and is lacking in mouse models. To aid the design of pre-clinical trials, new approaches are required to comprehensively characterise the medulloblastoma TIME and assess the impact of MYC-targeting agents on its constitution. To address this need, this project aimed to develop novel MB-specific deconvolution signatures built upon RNA-seq expression data, enabling comprehensive profiling of the MYC-MBGroup3 TIME in both human cohorts and genetically engineered syngeneic mouse models.

Method:

To construct a human deconvolution signature set capable of discerning between cancer, brain and infiltrating immune cell types, gene expression data from MB cell lines, astrocytes, oligodendrocytes, neurons, microglia and endothelial cells were combined with the LM22 dataset that covers 22 immune cell types. For the mouse signature, 58 reference profiles covering 14 immune cell types were combined with 8 cancer profiles from the GTML and GMYC models. Markers for each cell type were identified using CIBERSORTx. Each signature was validated using artificially generated pseudo-mixtures. For further validation, the correlation between estimated CD8 T-Cell proportion and cytolytic score was calculated. Cell-type proportions of 232 medulloblastoma tumours were then estimated using our human signature via CIBERSORTx. We also estimated cell-type proportion in the GTML model (n=11) following doxycycline-dependent MYCN regulation using our murine signature.

Results:

A human deconvolution signature set comprising 919 genes was constructed covering 28 cell types, whereas the murine signature comprised 2820 genes and covered 15 cell types respectively. Both signatures showed good performance in accurately estimating cell-type proportion. Correlation between synthetic pseudo mixtures and CIBERSORTx estimates was very high (Human: $R=0.998$, $p < 0.001$ / Mouse: $R=0.94$, $p< 0.001$). CYT score and estimated CD8 proportion were also positively correlated ($R=0.49$, $p < 0.001$). Application of the human signature to Group 3 and Group 4 medulloblastoma tumours revealed significant differences in immune cell infiltrate between subtypes. Application of the murine signature to GTML models also revealed differences in immune cell-type infiltration following MYCN modulation.

Conclusion:

We present the development of two deconvolution gene expression signatures, capable of accurately estimating immune cell infiltrates in human tumours and mouse models. Both signatures can be deployed to characterise the medulloblastoma TIME at high resolution, enabling us to comprehensively investigate its constitution in human tumours, and observe how treatments influence the TIME in experimental mouse models. These advances provide a rational basis to enable investigations which will inform the development of novel immunomodulatory therapeutic approaches for MYC-amplified Group3 medulloblastoma.

Does LED photobiomodulation therapy have a role in the supportive care management of oral mucositis in a paediatric oncology setting?

Ugo Offor[1], Stephanie Brown[1], Tasnim Arif[1]

[1] Department of Paediatric Haematology and Oncology, The Great North Children's Hospital, Newcastle upon Tyne

Background:

Mucositis is a common complication of systemic anti-cancer treatment and local radiotherapy with a high risk of morbidity and mortality. Patient-delivered photobiomodulation (PBM) using infra-red LED therapy has been shown to be a low risk and cost-effective treatment option in adult cancer patients for preventing oral mucositis and reducing its severity. There is sparse data on its efficacy in children and young people with cancer. This quality improvement (QI) project aimed to determine if PBM with LED therapy has a role in the prevention and treatment of oral mucositis in a paediatric oncology setting.

Method:

A local Trust guideline for delivering PBM therapy was rolled out in our primary treatment centre (PTC) in April 2022. Prospective demographic and clinical data were collected for all patients requiring either prophylactic or therapeutic PBM during admission to our oncology ward between 1st April 2022 – 30th September 2022. Route of nutrition, type of analgesia, and duration of treatment were used to assess the severity of mucositis episodes and its response to PBM therapy where applicable. Similar retrospective data were collected for any patient admitted for mucositis supportive care in the 6 months preceding the introduction of PBM therapy in order to facilitate a "before" and "after" comparison. Patients and their families were also invited to complete an anonymous feedback survey on their experience of using PBM.

Results:

A total of 84 admission episodes in 36 patients were eligible for either prophylactic (67/84) or therapeutic (17/84) PBM therapy. Intervention was delivered as per Trust guideline in 60/84 (71%) of admissions. This included 13 episodes of mucositis in 9 patients. All patients eligible for therapeutic PBM had received anthracycline-based chemotherapy with(out) high-dose methotrexate prior to developing mucositis. All patients were neutropenic on admission, with a related febrile episode seen in 30% of cases. Mouth swabs were positive for either HSV, Candida or Klebsiella in 4/13 (30%) of mucositis episodes. Patient-controlled analgesia (PCA) with morphine and/or ketamine was required in 47% of admissions prior to the introduction of PBM compared to 23% in patients receiving PBM therapy. Similarly, a change in route of nutrition was required for 76% vs 50% of admission before and after the introduction of PBM therapy respectively. This was driven by dietary support with total parenteral nutrition (TPN) in 49% of admissions in the "before" group compared to 14% in the "after" group. The median duration of treatment for mucositis was 6 days (range = 2 – 22 days) prior to PBM therapy compared to 5 days (2 – 15 days) during the subsequent period. Eighty-three percent of patients found the LED system easy to operate and all of them indicated a willingness to use it again.

Conclusion:

This QI project offers some objective evidence supporting the use of PBM with LED therapy as a supportive care measure to reduce the severity of oral mucositis in paediatric oncology patients. It is well tolerated in this cohort with high patient acceptability as a treatment option.

Acquired resistance to temozolomide in the Th-MYCN mouse as a clinically-relevant platform to evaluate novel therapeutic strategies against high-risk neuroblastoma

Sara Heuss[1], Giuseppe Barone[1,2,3], Konstantinos Zormpas-Petridis[1], Simon P. Robinson[1], Paul Workman[1], Yann Jamin[1,4]

[1] The Institute of Cancer Research
[2] The Royal Marsden
[3] Great Ormond Street Hospital for Children
[4] Scintica

Background:

The application of the mouse hospital and co-clinical concept represents a clear paradigm shift in neuroblastoma translational research. This approach integrates more advanced mouse modelling, such as genetically engineered mouse (GEM) models and patient-derived xenograft to accelerate the discovery and evaluation of novel therapeutic strategies and helps shape the clinical trial pipeline priorities for children with high-risk relapsing/refractory neuroblastoma. Yet there is a lack of characterized *in vivo* models that emulate the clinical refractory disease, which could affect the predictability of the mouse hospital approach. The Th-MYCN mouse is the most established genetically engineered model of neuroblastoma, which have been shown to recapitulate the major genetic and patho-physiological feature of high-risk MYCN-amplified childhood disease and as represents a relevant model to provide mechanistic insights for the development and evaluation of MYCN-targeted therapeutics. However, its sensitivity to frontline chemotherapy agent such as cyclophosphamide is reminiscent of the chemo-sensitivity of MYCN-amplified neuroblastomas following induction therapy rather than the chemo-refractory disease. Here, we describe the generation of a temozolomide (TMZ) resistant model using dose escalation.

Method:

Homozygous Th-MYCN mice with palpable tumours were enrolled for initial MRI screening. MRI was performed on a 7T Bruker horizontal bore Microimaging system (Bruker Instruments, Ettlingen, Germany) using a 3cm birdcage volume coil. When tumour volume reached ~ 1000 mm3, mice were enrolled on the first cycle consisting of daily dose of 6 mg/kg of TMZ via oral gavage for 5 days followed by two days off. The dose of 6m/kg was established to cause significant anti-tumour activity, yet without causing complete response. Dose was increased by 50% if the tumour progress during the subsequent cycles until tumour growth could not be controlled anymore. At day 5 of the last cycle, mice were either i) sacrificed and tumour excised for molecular and pathological analysis or ii) treated with a high dose of TMZ (50 mg/kg via oral gavage, n=4).

Results:

We demonstrate that the Th-MYCN model of neuroblastoma acquired resistance to cyclic treatment with TMZ, recapitulating the known molecular and pathological hallmarks associated with TMZ resistance, including increased expression of O6-methylguanine DNA methyltransferase (MGMT), a DNA repair a DNA repair enzyme,
which removes the TMZ-mediated cytotoxic O6-methylguanine (O6MG) DNA lesions.

Conclusion:

Temozolomide is a second-line chemotherapy agent, which shows moderate tumour control against refractory neuroblastoma and represents, once resistance occurs, the backbone chemotherapy for the introduction of novel therapeutic strategies in European paediatric clinical trials. Here, we have generated a temozolomide resistant model as a clinically relevant platform to evaluate novel therapeutic strategies against high-risk neuroblastoma.

Prevalence of childhood cancer survivors in Europe: A scoping review

De Paula Silva[1], N., Gini, A., Dolya, A., Colombet, M., Soerjomataram, I., Youlden, D., Stiller, C., Steliarova-Foucher, E., and CRICCS Corsortium

[1] International Agency for Research on Cancer, Lyon, France

Background:

Childhood cancer survivors (CCS) require specialized follow-up throughout their lifespan to prevent or manage late effects of cancer treatment. Knowing the size and structure of the population of CCS is crucial to plan interventions.

Method:

We reviewed studies that reported prevalence of CCS in Europe. In this scoping review we searched for articles on Medline, Web of Science, and Embase using permutations of terms referring to childhood, cancer, survivors, prevalence, registries, and Europe. We followed PRISMA-ScR guidelines to select studies and The Joanna Briggs Institute Prevalence Critical Appraisal Tool to evaluate their quality.

Results:

From 1237 identified studies published between 1989-2022, 13 were included. Limited-duration prevalence (LDP) for all childhood cancers, assessed in four studies, varied between 450 and 1240 persons per million. Complete prevalence (CP) of survivors of any childhood cancer except skin carcinomas, reported in three studies, varied between 730 and 1110 persons per million. CP of survivors of embryonal tumours, estimated in six studies, varied between 48 and 95 persons per million.

Conclusion:

Information on prevalence of CCS in Europe is fragmented and inconsistent. The large variations in LDP and CP estimates were linked to differences in population, prevalence measure, incidence period, index date, age at diagnosis and prevalence, cancer types, sex, and, for LDP studies, also the length of follow-up. Standard methodology is needed to systematically monitor CCS prevalence in Europe, allow international comparison, and ultimately provide data to help address survivors' needs.

Second primary neoplasms among childhood cancer survivors in Europe: A population study

Neimar De Paula Silva[1], Andrea Gini[1], Murielle Colombet[1], Eva-Steliarova-Foucher[1]

[1] International Agency for Research on Cancer, Lyon, France

Background:

Childhood cancer survivors (CCS) are at a high risk of developing second primary neoplasms (SPN). Within the Cancer Risk in Childhood Cancer Survivors (CRICCS) study, funded by Children with Cancer UK, we assessed the incidence of SPN among CCS in Europe.

Method:

We pooled data from 73 population-based cancer registries operating in 31 European countries that provided data to the Automated Childhood Cancer Information System database over variable time periods ranging between 1953 and 2011. We included only malignant tumours that were either diagnosed in patients younger than 20 years or were subsequent tumours in these patients. All cancers were classified by the International Classification of Childhood Cancer. For the 5-year CCS we computed incidence rate of SPN per 100,000 person years and cumulative incidence of SPN.

Results:

The 148,759 5-year CCS were followed-up for a median of 13.6 years and 2.4 million person-years, which gave rise to 1,935 SPN. The median age at SPN diagnosis was 27 years. Incidence rate of all SPN was 81.4 per 100,000 person-years. Most common SPN among 5-year survivors were carcinomas (59.5% of the 1,935 SPN), soft tissue sarcomas (8.4%), and central nervous system tumours (8.3%). We also noted common sequences of a CNS tumour in leukaemia patients (3.8% of all SPN) and bone tumour in retinoblastoma patients (2.3%). The cumulative incidence of SPN increased with time since diagnosis from 0.4% at 10-years to 5.5% at 40-years. The largest cumulative incidence of SPN at 40 years after diagnosis was seen in children diagnosed with lymphoma. Second tumours developed in CNS and bone at a younger median age (14 years) than second leukaemia (19), soft-tissue sarcomas (23) or carcinomas (32).

Conclusion:

Our study shows that SPN incidence among CCS increases with time and age and that the type of the first primary tumour may determine the SPN type in some patients. These findings highlight the importance of long-term follow-up of CCS, both in medical setting and in population-based cancer registries. Through the CRICCS study we encourage the registries to collect data required to study risk of SPN in childhood cancer survivors, including determinants of risk such as treatment for first cancer and predisposing syndromes. Standardised routine collection and pooling of such data could contribute to SPN prevention.

A new method of estimating Prevalence Of Childhood Cancer Survivors (POCCS): example of the 20-year prevalence in the Netherlands

Eva Steliarova-Foucher[1], Andrea Gini[1], Murielle Colombet[1], Neimar de Paula Silva[1], Otto Visser[1], Danny Youlden[1], Isabelle Soerjomataram[1], Charles A Stiller[1], and the CRICCS Consortium

[1] International Agency for Research on Cancer, Lyon, France

Background:

Estimating the number of childhood cancer survivors (CCS) is crucial for cancer control, including clinical guidelines. To compare estimates across countries despite data sharing restrictions, we propose a new method of computing limited-duration Prevalence Of Childhood Cancer Survivors (POCCS) using aggregated data.

Method:

We developed a Markov model (MM) that simulates, for each calendar year and birth cohort in a population, the proportion of individuals in the following health states: healthy, newly diagnosed with cancer, surviving with cancer, and deceased. Transitions between health states were informed using annual sex- and age-specific incidence rates, conditional 1-year net survival probabilities from the Netherlands Cancer Registry (1989-2011), and annual mortality probability by sex and age group for the Netherlands from the Human Mortality Database. Applying a MM, we computed 20-year prevalence of CCS. The resulting POCCS estimates, stratified by sex, were compared with SEER*Stat estimates derived from individual cancer records from the same registry.

Results:

In 2011, POCCS predicted 654 males (95% confidence interval [95%CI]: 637-672) and 539 females (95%CI: 523-555) per million persons living in the Netherlands after childhood cancer diagnosed within the previous 20 years. Using SEER*Stat, the 20-year prevalence was 665 males (95%CI: 647-683) and 544 females (95%CI: 529-560) per million persons on 1st July 2011.

Conclusions:

Using the POCCS model and aggregated cancer data, our estimates of CCS limited-duration prevalence were consistent with those computed by a standard method requiring individual cancer records. The POCCS method provides relevant information for planning follow-up and care for CCS.

Systematic assessment of prevalence of childhood cancer survivors in the WHO European region

Andrea Gini[1], Neimar de Paula Silva[1], Murielle Colombet[1], Anastasia Dolya[1], Charles Stiller[1] and Eva Steliarova-Foucher[1] on behalf of data contributors

[1] International Agency for Research on Cancer, Lyon, France

Background:

Quantifying the prevalence of childhood cancer survivors (CCS) is essential for planning health care in a population. In the absence of a comparable data on prevalence of CCS in Europe we developed estimates for 40 countries of the WHO European region.

Method:

We used the Prevalence Of Childhood Cancer Survivors (POCCS) model – developed within the Cancer risk in childhood cancer survivors (CRICCS) project – to estimate prevalence of survivors who were diagnosed with cancer before 15 years of age. The model was informed by aggregated cancer data from the Automated Childhood Cancer Information System (ACCIS) database, data on cancer mortality and population extracted from the Human Mortality Database (HMD) and the United Nations population estimates, depending on availability of the required data in each country. We computed 10-year limited duration prevalence of CCS in 2011 for the WHO European region and four sub-regions.

Results:

In the WHO European region, we estimated 125,021 10-year CCS alive in 2011. This corresponds to a 10-year age-standardised prevalence proportion (ASPP) of 312 per million general population. The highest number of CCS (43,165) lived in the Eastern European region, where the crude prevalence proportion (CPP) was lowest (147 per million). In the other regions, CPP varied from 183 per million in Southern Europe to 189 per million in Northern Europe and British Isles. The 10-year ASPP was highest in Southern Europe (348 per million), followed by Western Europe (339 per million), Northern Europe and British Isles (310 per million), and lowest in Eastern Europe (276 per million).

Conclusions:

This study is the first comprehensive assessment of prevalence of CCS in Europe, quantifying CCS prevalence in Europe. This information will assist policymakers to allocate health resources required to support the CCS population.

Expanding the contribution of population-based cancer registries to survivorship research: The cancer risk in childhood cancer survivors (CRICCS) study

Steliarova-Foucher E[1], de Paula Silva N[1], Gini A[1], Colombet M[1], Dolya A[1], Hjorth L[2], Pritchard-Jones K[3], Stiller CA[4] and the CRICCS Consortium

[1] International Agency for Research on Cancer, Lyon, France
[2] Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Paediatrics, Lund, Sweden
[3] University College London, UCL Great Ormond Street Institute of Child Health, London, UK
[4] National Disease Registration Service, NHS England, UK

Background:

Childhood cancer survivors (CCS) are subjected to an increased cancer risk, which may be amenable to prevention. Pooling data collected by population-based cancer registries could shed light on determinants of the risk of second primary neoplasms (SPN) in CCS and thus indicate possibilities of SPN prevention.

Method:

Supported by the international consortium, we set up the study Cancer Risk in Childhood Cancer Survivors (CRICCS, criccs.iarc.who.int). Over 500 registries in 147 countries worldwide were invited to join the study by describing registration process and data they collect, and by providing records of first cancers diagnosed during childhood, its treatment, any SPN, and any predisposing syndromes likely to explain variations in SPN risk. We developed a new method to estimate the size of the population of CCS in Europe, which was not systematically evaluated until now. We piloted the methodology of estimating risk of SPN using data collected previously for Automated Childhood Cancer Information System (ACCIS) and calculating standard incidence ratios (SIR) of observed to expected SPN. For each cancer registry, the expected number of SPN was computed by applying the country-specific incidence rates, retrieved from Cancer Incidence in Five Continents (ci5.iarc.fr/CI5plus), to person-years of cumulative follow-up of individual patients.

Results:

Overall, 163 registries in 70 countries contributed to the CRICCS study either by submitting a questionnaire informing about collected data (N=155 registries) or by sending at least one data file (N=114). The datasets of certain registries included information on follow-up for vital status (N=105) or on treatment (N=47). Eight registries provided some information on predisposing characteristics. Most participating registries (93 of 163) operate in countries with very high human development index. Based on the newly developed method named Prevalence of Childhood Cancer Survivors (POCCS) we estimated that 125,021 10-year CCS were living in 2011 in the populations of 53 countries of the WHO European Region. Preliminary analysis, assessing the cancer risk during an approximate period 1988-2012 in 34 European populations in which childhood cancer patients were followed for a median of 13.5 years, showed a triple risk of SPN in 5-year CCS when compared with the general population. An inventory of needs for harmonisation of data collected by registries was developed.

Conclusions:

The CRICCS study targets very rare events and therefore requires pooling data from large populations. Over 150 registries demonstrated interest in this collaboration, although many encountered barriers to participation, such as low priority given to this research, inability to share data, or limited resources. The paucity of available data influences the results of the analyses. This study aims to effectively define and use data that could be routinely collected by population-based cancer registries to describe the causes of the additional cancer risk specific to CCS. High-quality large-scale information will contribute to reducing the cancer burden among CCS.

International variation in child health surveillance and acute care practices: A mixed methods analysis

Angela Lopez-Cortes[1], Aisha Al Mahdy[1], Masako Shimato[1], Laura Botta[2], Fabio Didonè[2], Adela Canete[3], Charles Stiller[3], Lisa L. Hjalgrim[3], Zsuzsanna Jakab[3], Bernward Zeller[3], Gemma Gatta[2], Kathy Pritchard-Jones[1] and The BENCHISTA Project Working Group.

[1] UCL Great Ormond Street Institute of Child Health, University College London, London,UK.
[2] Fondazione IRCCS "Istituto Nazionale dei Tumori di Milano", Milan, Italy.
[3] BENCHISTA Project Management Team.

Background:

Variation in childhood cancer (CC) survival rates observed across countries might be partly explained by differences in pathways to medical attention and timely diagnosis for symptomatic children. This study aims to assess current evidence in child health surveillance and acute care practices and to perform a descriptive comparative analysis of child health practices in countries participating in the International Benchmarking of Childhood Cancer Survival by Stage – The BENCHISTA Project.
BENCHISTA is a collaboration between 67 population-based cancer registries that collects standardised data on tumour stage at diagnosis for six childhood solid tumours.

Method:

A mixed methods approach comprising 1. A comprehensive literature review of articles published in the last decade using five databases and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Terms including paediatrics/child, diagnosis, cancer, population, surveillance, were used to create the search strategy. Two independent reviewers screened abstracts for full text selection/data extraction. A third reviewer (paediatric oncology expert) resolved conflicts. 2. A semi-structured questionnaire was created on a secure platform to collect standardised data on child health practices within each participating country. It focused on routine surveillance check-ups (frequency and type of provider) and route to medical attention for acute symptoms. Information on required paediatric training of front-line practitioners was also collected. The questionnaire was addressed to one general practitioner and one general paediatrician to provide relevant information about the country's national health policies and practices.

Results:

2,788 articles were screened; 30 articles met eligibility criteria for inclusion. Three main topics were identified: pathway to diagnosis, awareness of alarm signs/symptoms of CC (parents and professionals) and factors affecting the timely diagnosis of serious childhood illnesses including cancer. 28 studies evidenced disparities in the routes used to detect serious illnesses including cancer (during routine child checks, screening of children with a predisposition syndrome or at hospital due to urgent or out-of-hours assessment). 19 studies evidenced differences in symptom awareness and
healthcare-seeking behaviours within population sub-groups. 27 studies explored factors affecting timely diagnosis of serious illnesses including lack of knowledge of risks associated with specific symptoms and the impact it may cause to the referral pathway, scarcity of guidance on high-risk signs/symptoms and lack of paediatric training of front-line personnel providing childhood routine and acute care, among others. The questionnaire was piloted, and vocabulary refined. 51 answers from practitioners from 25 countries within and outside Europe were obtained. Noticeable variation in child health surveillance practices, particularly in the number of universally offered check-ups with physical examination provided in children under 5 years old (median: 10 and range:2-21) was found. Validation against national published guidance was performed.

Conclusions:

Noticeable variation in terms of frequency of routine child health surveillance and in access to assessment by a paediatrician for children with acute symptoms was found across countries. Similar variation in available guidelines to raise awareness of childhood cancer or serious conditions "alarm symptoms" is evident. The results may provide guidance to categorise countries for interpretation of variation in stage at diagnosis in the BENCHISTA Project.

BENCHISTA project: International benchmarking of childhood cancer survival by tumour stage - preliminary results for Wilms tumour

Kathy Pritchard-Jones[1], Angela Lopez-Cortes[1], Adela Canete[3], Charles Stiller[3], Lisa L. Hjalgrim[3], Zsuzsanna Jakab[3], Bernward Zeller[3], Fabio Didonè[2], Laura Botta[2], Gemma Gatta[2], and The BENCHISTA Project Working Group.

[1] UCL Great Ormond Street Institute of Child Health, University College London, London, UK.
[2] Fondazione IRCCS "Istituto Nazionale dei Tumori di Milano", Milan, Italy.
[3] BENCHISTA Project Management Team.

Background:

Differences in childhood cancer (CC) survival rates across countries might be explained by variation in stage at diagnosis. The BENCHISTA project aims to understand this variation and stimulate the application of the internationally recognised Toronto Guidelines (TG) for documentation of tumour stage and other non-stage prognostic factors (NSPs) by population-based cancer registries (PBCRs) to the most common solid paediatric cancers, including Wilms tumour (WT).

Method:

Participating PBCRs collected all cases of six solid tumours (0-14yrs: Neuroblastoma, Medulloblastoma Wilms tumour; 0-19yrs: Rhabdomyosarcoma, Osteosarcoma and Ewing sarcoma) diagnosed between 2014-2017 and applied TG at diagnosis with follow-up for survival for at least 3yrs. Other NSPs including presence of anaplasia, treatments given and if relapse occurred were collected as optional variables to test feasibility for PBCRs to access these at a population-level. Depersonalised, patient-level datasets with staging information according to available clinical sources were submitted to the Istituto Nazionale dei Tumori, Milan, for compilation into a master database. Survival analyses used standard Kaplan-Meier methods.

Results:

67 PBCRs from 24 European countries and Australia, Brazil, Japan and Canada are participating. Agreement on data format was reached by March 2021 but it required further 18 months to finalise and sign-off the project-specific Data Transfer Agreement (DTA). Only 41 PBCRs required a DTA to share this highly depersonalised routine healthcare dataset according to their national/regional data protection regulations and country-specific legislation. By May 2023, 10,504 cases had been received (~95% of total expected), of which 2,109 (20%) were WT. Completeness of tumour stage at diagnosis for WT was 97% (Tier 1) and 95% (Tier 2). At a population-level, 19% had metastases at diagnosis and 5% had bilateral disease. Initial treatment approach was immediate surgery in 465 (22.1%) and pre-operative chemotherapy in 1,644 (77.9%). Presence or absence of anaplasia could be documented in 57% of cases, among whom the reported prevalence of anaplasia was 5%. Overall 3yr survival (OS) was 93% (95%CI: 92-95), ranging from 97.8% (stage I/yI) to 83.2% (stage IV).

Conclusion:

Heterogeneity in data availability and challenges related to data transfer/sharing processes were encountered. Despite this, PBCRs could achieve data collection and apply TG to a high proportion of WT cases. Access to NSPs requires close cooperation with clinicians and clinical registries. The BENCHISTA Project has established a large multi-disciplinary collaboration producing standardised data on stage at diagnosis. This will enable comparative analyses for a deeper understanding of the underlying reasons for international variations in survival rates.

Dissecting the heterogeneity of paediatric spinal ependymoma by integrative genomics analysis

Anbarasu Lourdusamy[1], Omar Mohammed[1], Rebecca Chapman[1], Omar Ahmad[1], Richard Grundy[1]

[1] Children's Brain Tumour Research Centre D30, Medical School, Queen's Medical Centre, University of Nottingham

Background:

Paediatric spinal ependymomas are rare but still represent the second most common spinal cord tumours in children and adolescents. Less representation and limited sample size in previous studies highlight the critical need for comprehensive profiling of spinal ependymomas in the paediatric population. Considering that ependymomas in children are biologically distinct from their adult counterparts, our study aimed to dissect the molecular heterogeneity of spinal ependymomas in children.

Method:

In this retrospective study, we have collected tumour samples from 27 spinal ependymoma patients younger than 18 years (11 girls and 15 boys). We carried out the histological review, DNA methylation, gene, and microRNA (miRNA) expression profiling, and performed integrative analyses.

Results:

Unsupervised analysis with methylation data revealed two distinct molecular subgroups, SP-MPE (n = 18) and SPEPN (n = 9). Copy numbers derived from DNA methylation arrays revealed subgroup-specific genetic alterations and showed that SP-EPN tumours lack MYCN amplification. Gene expression profiling revealed distinct transcriptomic signatures, including overexpression of genes involved in oxidative phosphorylation in SP-MPE. We discovered widespread decreases in DNA methylation at enhancer regions that are associated with the expression of oncogenic signalling pathways in SP-MPE. Transcription factor motifs for master regulators, including HNF1B, PAX3 and ZIC3, were significantly overrepresented in probes specific to distal regulatory regions in SP-MPE. Furthermore, the expression of long non-coding RNAs (lncRNA) differed significantly across these subgroups, notably, JAKMIP2-AS1 showed high expression in SP-MPE. The co-expression network analysis between lncRNA and mRNA identified 151 lncRNAs and 206 mRNAs for SP-EPN and showed enrichment for cell junction organization, cell-cell adhesion, and several neuronal system-related processes, including neuron development, migration, and differentiation. In contrast, 343 mRNAs in the SP-MPE network showed enrichment for various metabolic-related pathways, including the small molecule metabolic process, carboxylic acid metabolic process, purine-containing compound metabolic process, and generation of precursor metabolites and energy.

Conclusion:

In summary, our study highlights the substantial heterogeneity in paediatric SPEN. It uncovers novel lncRNAs and their target genes and pathways specific to two subgroups of paediatric SPEN, providing a foundation for future therapeutic strategies.

World-wide survival trends for young patients aged-24 years diagnosed with lymphoma during 2000-2014 (Concord-3)

Naomi Ssenyonga[1], Michel P Coleman[1,2], Claudia Allemani[1], on behalf of the CONCORD Working Group

[1] Cancer Survival Group, London School of Hygiene and Tropical Medicine, UK
[2] Cancer Division, University College London Hospitals NHS Foundation Trust, London, UK

Background:

CONCORD-3 highlighted global variations in five-year survival from lymphomas in children (0-14 years) and lymphoid malignancy in adults (15-99 years). Here, we examine world-wide trends in survival from lymphoma and its morphological sub-types in young patients (0-24 years) diagnosed during 2000-2014 in 62 countries.

Method:

We grouped patients by age as children (0-14 years), adolescents (15-19 years) and young adults (20-24 years). We categorised lymphoma sub-types by the International Classification of Childhood Cancer (ICCC-3), updated with ICD-O-3 codes. We estimated net survival up to 5 years by age and sub-type, using the non-parametric Pohar-Perme estimator. To control for background mortality, we used life tables by country/region, single year of age, single calendar year and sex, and where possible by race. All-ages survival estimates were standardised using the marginal distribution of young patients included in the analysis.

Results:

We analysed data for 41,177 (34.3%) children, 33,904 (28.2%) adolescents and 45,039 (37.5%) young adults. The most common sub-types were Hodgkin lymphoma (54.1%) and Non-Hodgkin (excluding Burkitt) (32.0%).

Age-standardised 5-year net survival in children, adolescents and young adults diagnosed during 2010-2014 varied widely, from below 60% in Chile to over 95% in Belgium, Germany, Iceland, Norway, Slovenia and Switzerland. Individuals with Hodgkin lymphoma experienced higher survival, with a global range from 70% to over 95%. The difference in survival between children and adolescents decreased over the period 2000-2014. Nonetheless, the gap in survival between high-income and low- and middle-income countries persisted.

Conclusion:

This study offers the first world-wide picture of the characteristics and trends in survival from lymphomas in children, adolescents and young adults. Our results show that survival is systematically higher for children and adolescents than in young adults, world-wide. Exploring trends in survival is an important indicator of the quality of management of cancer in this age range.

Investigating immunological risk factors for post-transplant lymphoproliferative disease: The immunology of thymectomy and childhood cardiac transplant (ITHACA) study

Ugo .T. Offor[1,2]; Paolo Hollis[3]; Heather .M. Long[4]; Milos Ognjanovic[5]; Jacob Simmonds[3]; Abbas Khushnood[6]; Zdenka Reinhardt[6]; Andrew Gennery[7]; Chris .M. Bacon[1,8]; Simon Bomken[1,2]

[1] Wolfson Childhood Cancer Research Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom. [2] Department of Paediatric Haematology and Oncology, The Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust. [3] Department of Cardiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom. [4] Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom. [5] Department of Paediatric Nephrology, Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom. [6] Department of Cardiopulmonary Transplantation, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom. [7] Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom; Department of Paediatric Immunology and Haematopoietic Stem Cell Transplantation, The Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom. [8] Department of Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Background:

Paediatric heart transplant (PHTx) patients are disproportionately affected by EBV-driven post-transplant lymphoproliferative disease (EBV-PTLD) compared to other solid organ recipients. There is limited understanding of the immunological factors that may contribute to disease ontogeny in this high-risk group. We have previously shown that pre-existing congenital heart disease and early thymectomy at < 1 year old are significant risk factors for developing EBV-PTLD. This multicentre prospective cohort study aims to examine the key immunological differences that are associated with early thymectomy and long-term iatrogenic immunosuppression, their impact on the temporal immune response(s) to an EBV infection and subsequent risk of EBV-PTLD.

Method:

The study cohort will consist of 34 PHTx, 6 renal transplant (RTx) patients, and age-matched healthy controls (aged 0-18 years) stratified into early (<1-year) vs late (>1-year) vs non-thymectomy groups. Prospective and sequential immune monitoring of transplant recipients will be performed using peripheral blood samples taken before transplant and at 3-, 6-, 12- and 24 months post-transplant. Single cell analysis of circulating immune cells and enumeration of EBV-specific T-lymphocytes will be conducted using high dimensional spectral flow cytometry and HLA-restricted MHC I/II tetramers respectively. The functional status of EBV-specific T-lymphocytes will be determined by ELISpot assay for interferon gamma activity. EBV antibodies and viral load will also be monitored at each of the pre-defined study time points.

Results:

The ITHACA study opened in March 2022 (ISRCTN10096625). Patient recruitment is currently ongoing. Thirty-one patients have been enrolled to date, with 22 participants receiving a primary organ transplant. A validated 26-colour flow panel has been developed for deep immunophenotyping of circulating lymphocytes, NK/T cells, and antigen presenting cells (monocytes and dendritic cells). This panel is complemented by a 30-colour targeted T-cell panel that includes multiple markers for cellular exhaustion and senescence (PD-1, CTLA4, LAG-3, TIM-3). Patient-matched HLA-restricted tetramer pools containing immunodominant EBV lytic/latent viral epitopes have been developed in collaboration with the Tetramer Core Facility at the National Institutes of Health (NIH), USA.

Conclusion:

The ITHACA study is the first In Vivo chronological mapping of immune reconstitution in thymectomised transplant patients and their subsequent response to EBV exposure. It will provide critical insight to the complex immunological mechanisms that underpin the development of EBV-PTLD. Sample analyses will help to support the identification of immune signatures and biomarkers that are risk predictive. These parameters can be explored to aid future patient risk-stratification and facilitate the development of clinical pathways that mitigate PTLD risk.

Children with Cancer UK
0800 222 9000
research@childrenwithcancer.org.uk
childrenwithcancer.org.uk

childrenwithcanceruk
@CwC_UK_Research
childrenwithcanceruk

Registered office
Third floor, 21-27 Lamb's Conduit Street
Holborn, London, WC1N 3NL

Registered charity number. 298405.
A company limited by guarantee.
Registered in England no. 4960054