7th December 2018 – version 2

Key Dates
Outline Applications by 25th January 2019 for shortlisting
Invited Full Applications by 30th March 2019

2018 Research Grant Call

£2.5 million Grant Call for investigations into causal and promotional factors and possible preventative actions regarding childhood and young person cancer

In a speech on 5th November 2018, the Secretary of State for Health and Social Care, the Rt Hon Matt Hancock, MP, stated: "We're here to talk prevention. And if there's one thing that everybody knows 'prevention is better than cure'. Prevention saves lives and saves money.

Full text: https://www.gov.uk/government/speeches/prevention-is-better-than-cure-matt-hancocks-speech-to-ianphi

Children with Cancer UK's Aims include:

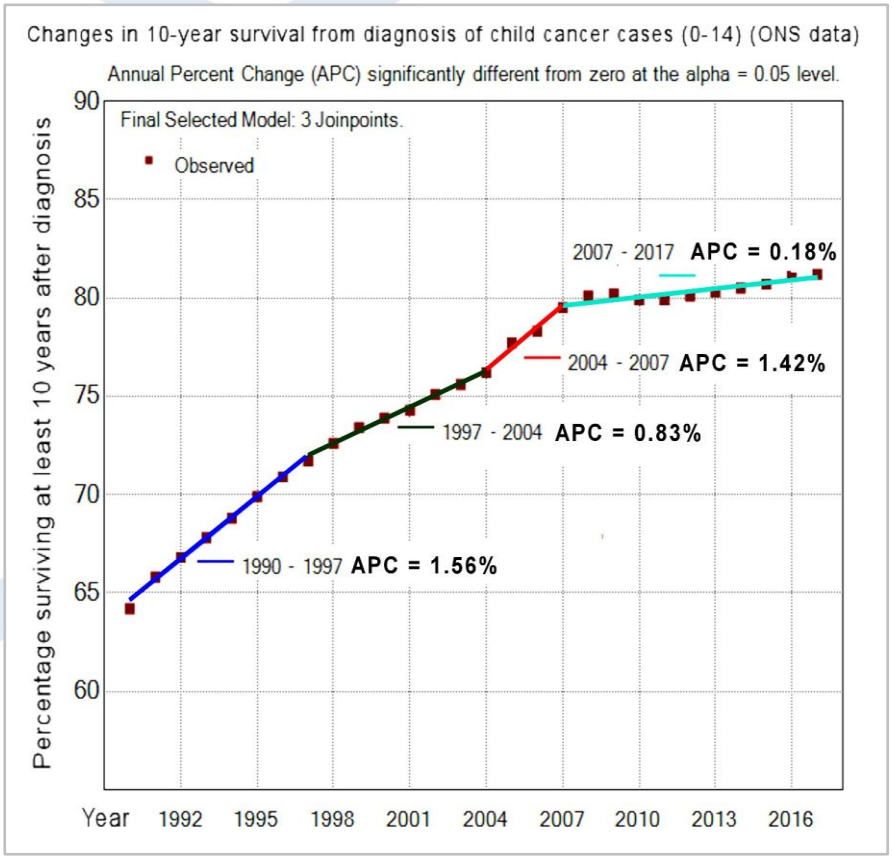
- To improve knowledge of the genetic and environmental causes and biological mechanisms of paediatric and young person cancers
- To identify diagnostic and prognostic biomarkers for paediatric and young person cancers to help develop targeted treatments and discover causal factors and help prevent cancer

In 1987, just before he died of leukaemia, 14 year-old Paul O'Gorman asked his father, Eddie, "Dad, why leukaemia, why me?" and Eddie had to reply "I don't know son. Nobody knows". Paul responded "Please find out, dad, and help stop other children developing cancer". So his parents, Eddie and Marion, started fundraising with the aim of supporting three-fold action: "Cause, Care and Cure".

In 1988, Diana, Princess of Wales, persuaded Eddie and Marion to start their own charity so that they could focus their funding on these actions.

Since then, Children with Cancer UK has raised over £240m to help do just that. Over that time treatment has greatly improved and overall survival has increased from 60% to 80% of children who develop cancer. Treatments have also become kinder, resulting in fewer long-term adverse health impacts in those who survive.

But, as shown on the graph, despite all the enormous amount of research into treatment there has been little improvement in long-term survival over the last ten years.



Children with Cancer UK 51 Great Ormond Street London WC1N 1JQ 0207 404 0808
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In recent years there have been some significant advances in understanding environmental and lifestyle factors that affect the risk of a child developing cancer.

There is good evidence of risk associated with some chemical exposures, such as from air pollution, pesticides, fire retardants and agricultural chemical residues in food. Natural background radiation, usually resulting in unavoidable exposure, is estimated to account for between 15 and 20% of the UK childhood leukaemia incidence. There is also some concern about exposure to electric and magnetic fields and non-ionising radiation, especial as regards cancer promotion. At the same time a number of lifestyle factors appear to protect against leukaemia risk and possibly other cancers in childhood.

Funding from Children with Cancer UK in 2007 helped to launch the Childhood Leukaemia International Consortium (http://circle.berkeley.edu/research/childhood-leukemia-international-consortium/), CLIC, which sponsors research and brings together epidemiological data and DNA samples from different research studies carried out in many different countries for leukaemia and other cancers. Pooling all of this detailed information gives researchers a unique opportunity to fill the gaps in our understanding of how environmental and genetic factors might cause or promote cancer in children. We currently fund the CLIC database at the International Agency on Cancer (IARC) in France.

Every year now about 2000 children (0-14) and 2500 young people (15-24) develop malignant cancer in the UK. It is clear that we need to press forward with high quality research into determining causal and promotional factors for child and young person cancer. Little time and money is spent at present on reducing preventable causes.

If we could have a similar success to the improvement in treatment over the past 30 years (20%) we would prevent about 900 cases per year! Even a 10% reduction would prevent about 450 new cases (and victims) every year.

Identifying, and then avoiding, environmental and lifestyle factors associated with the development of cancer will also offer the chance to reduce the likelihood of relapse after successful treatment.

Virtually no research is currently being funded in the UK on environmental (mostly man-made) carcinogen research and on what proportionate precautionary actions could be taken to reduce the toxic burden that may help to prevent child and young person cancer.

While we will also continue to fund leading-edge research into better treatment, this 2018 Grant Call is the first of a number which will fund key research into cause and prevention.

The rationale behind this grant call

In order to determine the causes of child and young person cancer (up to about age 24), we need properly to discover the chemical, radiological and biological mechanisms of action that lead to the development of cancer. Life is very complex and life processes are far from simple. The causes of cancer are multifactorial and include inherited genetics, epigenetic changes, damage by chemicals and ionising radiation, promotional effects of chemicals, non-ionising radiation, diet and lifestyle.

Using the latest techniques we are now able to look more deeply at the actors that have previously been reported as possibly/probably being related to the development and promotion of cancer.

To obtain better knowledge about the pollutants to which the foetus and infants are being exposed, we are interested in funding exposome assessments. This includes finding direct and indirect measures of known pollutants, or biomarkers of exposures to pollutants resulting from parental and personal lifetime exposures. These can be found in cord blood, in hair and sometimes in deciduous teeth of infants and young children. There has also been published work analysing metabolic signatures of multiple chemical pollutants in the urine of pregnant women.

Much of human development is completed during the first 1000 days following conception. Each system and organ has a critical period, often brief and *in utero*, during which initial development occurs. We know that children who develop leukaemia are usually born with a characteristic gene rearrangement (a genetic marker of leukaemia risk). We need to discover what toxic factors are present during foetal development that might provide a further leukaemia activation factor.

Some biomarkers result from defensive actions by living organisms in response to toxic contaminants in their environment. These can indicate biological changes resulting from stressors that may directly cause genotoxicity, immunotoxicity, energy metabolism impairments, endocrine disruption, etc. that could pre-dispose a person to the development or promotion of cancer. Some early work, that we would like expanded, has indicated DNA methylation as a potential mediator of early life exposures in the development of childhood acute lymphoblastic leukaemia and should help to provide clues to help develop preventative strategies.

This Grant Call is open to submissions seeking to investigate causal and promotional factors and possible preventative actions relating to the risk of cancer in children and young persons.

Here, in no particular order, are some of the specific areas that we are interested in funding.

1. Air pollution

Epidemiological studies in general continue to suggest an association between childhood cancer incidence and air pollution, notably from motor vehicle exhausts. However, many such studies have used nitrogen dioxide, NO_2 as the exposure metric. NO_2 is neither a carcinogen, nor an adequate marker of exposure to the carcinogenic component. In contrast, studies assessing exposure to carcinogens such as benzene and 1,3-butadiene show clearer association with childhood cancer. However, gaps in the knowledge remain on the particle size distribution of the carcinogenic component(s) of air pollution. Such knowledge is needed for assessment of the uptake by the body in general, including trans-placental transfer of inhaled carcinogens.

Suggested research area

Experimental determination of the size distribution of the carcinogenic component (specific carcinogens) of air pollution – from ultrafine to course particles (with emphasis on the ultrafine range). Determinations should be made in areas of high, medium and low ambient air pollution.

2. Air and other pollution - transplacental transfer and foetal exposure

Measurements of DNA damage in cord blood have been made in the NewGeneris project in relation to maternal dietary carcinogens. The approach used in this study could be extended to address exposure by maternal inhalation to the carcinogenic component of air pollution.

Suggested research areas

- Measurements of DNA damage in cord blood, in areas of high, medium and low exposure to air pollution.

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- Direct measurements of chemical pollutants in cord blood, in areas of high, medium and low exposure to air pollution. Some small investigations funded by the USA Environmental Working Group (a NGO) have found relative low levels of a wide range of known carcinogens in cord blood. It would be helpful to discover if this is the case in the UK.

Reference:
Kleinjans J, Botsivali M, Kogevinas M, Merlo DF,on behalf of the NewGeneris consortium. Fetal exposure to dietary carcinogens and risk of childhood cancer: what the NewGeneris project tells us.
BMJ2015;351:h4501. doi: https://doi.org/10.1136/bmj.h4501

3. The Exposome and its relation to child and young person cancer

The 'exposome' has been proposed as a new paradigm to encompass the totality of human environmental (meaning all non-genetic) exposures from conception onwards, complementing the genome. There are large challenges in developing the exposome concept into a workable approach for epidemiological research. These include:

(1) the accurate and reliable measurement of many exposures in the external environment

(2) the measurement of a wide range of biological responses in the environment inside the body

(3) addressing the dynamic, life course nature of the exposome.

Investigating and developing an understanding of the importance of the exposome offers a new and exciting paradigm for improvement and integration of currently scattered and uncertain data on the environmental component in disease aetiology. This should lead to a better understanding of the role of environmental risk factors in non-infectious disease and ultimately to better primary prevention strategies.

Reference:
Martine Vrijheid, The exposome: a new paradigm to study the impact of environment on health
https://thorax.bmj.com/content/thoraxjnl/69/9/876.full.pdf

4. Carcinogens in breast milk and infant formula milk

Santonicola et al (2017) have reported measurements of polycyclic aromatic hydrocarbons (PAHs) in both breast milk and infant formula milk in Italy. The levels found are of potential concern for consumer health. Similar studies should now be repeated for the UK population.

> Suggested research area
> Experimental determination and risk assessment of polycyclic aromatic hydrocarbons in breast milk and infant formula milk in the UK population

Reference:
Santonicola et al (2017) Comparative study on the occurrence of polycyclic aromatic hydrocarbons in breast milk and infant formula milk. Chemosphere 175:383-390. https://doi.org/10.1016/j.chemosphere.2017.02.084

5. Low level ionising radiation and carcinogenesis

Ionising radiation is a known cause of childhood leukaemia. We are open to suggestions for investigative work in this area regarding exposure to environmental and Computerised X-ray Tomography (CT scans) sources of ionising radiation.

6. Electric and magnetic fields and electromagnetic radiation

6.1 Power frequency magnetic fields have been reported to engender genomic instability in cells *in vitro*, in a manner similar to that known for ionising radiation (Luukkonnen et al 2014). Ionising radiation also exhibits the so-called "Bystander Effect" *in vitro*, in which DNA damage is found in nearby cells not directly exposed to ionising radiation.

Magnetic fields are also reported to release reactive oxygen species *in vitro*.

> Suggested research area
> Experimental investigation: Are there bystander effects associated with exposure to power frequency magnetic fields?

Reference:
Luukkonen J, Liimatainen A, Juutilainen J, Naarala J. 2014. Induction of genomic instability, oxidative processes, and mitochondrial activity by 50 Hz magnetic fields in human SH-SY5Y neuroblastoma cells.
Mut. Res. 760 (2014) 33– 41 https://www.sciencedirect.com/science/article/pii/S0027510713001991

6.2 Microwave radio frequency (RF) fields

In 2011 the International Agency for Research on Cancer (IARC) classified microwave RF exposure (primarily from modern wireless devices) as a Group 2B 'possible human carcinogen'. Since then increasing published scientific evidence suggests that it should now be classed at least as a Group 2A 'probable human carcinogen', or even as a Group 1 'known human carcinogen'.

In 2018 there were two landmark publications linking RF exposure to cancer. In the USA the $30m, 10-year, National Toxicology Program (NTP) confirmed evidence that mobile phone radiation could cause malignant glial cell cancer in rats (in the heart and brain). Also in 2018 the Ramazzini Institute published an RF exposure rat lifetime study which found results consistent with, and which reinforce, the NTP study results.

Further work is still necessary and we would be open to consider providing funding in this area.

References:
Falcioni L, Bua L, Tibaldi E, et al. (2018) Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission. Environ Res 165:496-503.
https://www.sciencedirect.com/science/article/pii/S0013935118300367

Wyde M, Cesta M, Blystone C, et al. (2016) Report of Partial findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposure). bioRxiv 055699. https://ntp.niehs.nih.gov/results/areas/cellphones/

https://www.niehs.nih.gov/health/materials/cell_phone_radiofrequency_radiation_studies_508.pdf

7. Breast milk or Formula feeding in the first 3 months of life

Does neonatal melatonin help to prevent early age child cancer? After receiving high levels of maternal melatonin during foetal growth, neonates cannot synthesise their own melatonin until after the first three months of infant life. A retrospective case-control comparison of breast milk and Formula milk as food in the first three months of life might help answer this question.

8. Obesity and childhood and young person cancer

A high Body Mass Index (BMI) at diagnosis is associated with poor overall and event-free survival among paediatric acute leukaemia (ALL and AML) patients. Targeted therapeutic approaches for obese paediatric leukaemia patients may potentially improve survival outcomes.

9. Cancer risk in survivors of childhood and young person cancer

It has been shown that childhood cancer survivors (CCS) have somewhere between a 5- and 50-fold increased risk of developing a different cancer after 10 or more years apparent event free survival. In a recent 5.6 year follow up study in Korea, Yu et al 2018 reported that CCS were found to be at a 20-fold higher risk of developing new malignant neoplasm compared to the general population. Ishida et al 2018, in a retrospective study of over 10,000 CCS survivors in Japan who were diagnosed between 1980 and 2009, found a high increased incidence of secondary cancer.

Suggested research area

What are the corresponding figures for the UK? If similar increases in risk are found, can these risks be mitigated against?

References:

1/. US National Cancer Institute (NCI) Childhood Cancer Survivor Study. https://dceg.cancer.gov/research/who-we-study/cohorts/childhood-cancer-survivors

2/. Ishida Y, Maeda M, Adachi S. et al. Secondary cancer after a childhood cancer diagnosis: viewpoints considering primary cancer, Int J Clin Oncol (2018) 23: 1178. https://doi.org/10.1007/s10147-018-1303-6 https://link.springer.com/article/10.1007/s10147-018-1303-6

3/. Yu et al 2018. Second malignant neoplasms after childhood cancer: A nationwide population-based study in Korea. PLoSONE 13 (11): e0207243. https://doi.org/10.1371/journal.pone.0207243

10. Prevention (including avoidance of new cancer in the future)

We would consider funding a monitored public health campaign similar to that in the US CIRCLE Programme described by Dr Mark Miller on Day 3 of the 2018 Children with Cancer UK conference. In the abstract to his talk, Dr Miller stated: "It is prudent to initiate programs designed to alter exposure to well-established leukaemia risk factors rather than to suspend judgment until no uncertainty remains if the goal is to protect children's health".

Primary prevention programmes for childhood leukaemia would also result in the significant co-benefits of reductions in other adverse health outcomes that are common in children, such as detriments to neurocognitive development (see the table in Dr Miller's abstract).

In 2018 a series of multi-author articles on preconceptual health were published in The Lancet with similar messages. One of these concludes:

> "We propose that the evidence for periconceptional effects on lifetime health is now so compelling that it calls for new guidance on parental preparation for pregnancy, beginning before conception, to protect the health of offspring."

They identify cardiovascular, metabolic, immune, neurological and other morbidities resulting directly from development processes in the foetus.

Reference:

Stephenson J, Heslehurst N, Hall J, *et al*, 2018, Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. Lancet, May 5; 391(10132):1830-1841. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30311-8/fulltext

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Invited full Applications by 30th March 2019

PLEASE NOTE:

Our project grants are intended to provide funds for the employment of suitably qualified staff and the purchase of essential equipment and consumables for projects lasting up to three years that address the objectives outlined above. In line with other UK medical charities, we do not contribute towards the cost of tenured posts nor can we contribute towards institutional overheads.

The maximum amount that can be applied for under this call is up to £250,000 for applications from a single institution, or up to £350,000 for collaborations involving more than one institution, though most grants will be for less than this. You may also apply for grants to fund shorter pilot investigations to test hypotheses.

Proposals must usually be submitted by a UK academic institution (university, hospital or research institute). We will consider funding international collaborations where researchers from a UK institution play a leading role. In the event that a grant is awarded to such a collaboration, the UK institution must take overall responsibility for management of the project and undertake to administer the funding.

Alasdair Philips (Trustee) and Professor Denis Henshaw (Scientific Director) and Joe Bryan (Grants Manager)

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