NCRC Annual Highlights April 2018 - March 2019

NCRC by numbers

No. of Active Grants
61

No. of Clinical Research Studies
47

Better Health for Children Through Research
No. of Funding Schemes available from the NCRC

- 2 Leadership Awards
- 15 Research Education Support Grants and IRC PhD Partnerships
- 26 Paediatric Research Project Grants
- 5 Innovation Awards
- 13 Clinical Research Fellowships

Total amount awarded to new research grants during the reporting period

€4.8m

No. of publications

236

No. of Irish Hospitals involved in NCRC supported research

9

- Beaumont Hospital
- CHI at Crumlin
- CHI at Tallaght
- CHI at Temple Street
- Cork University Hospital
- Rotunda Hospital
- St Vincent’s Hospital
- The Coombe Women & Infants University Hospital
- The National Maternity Hospital Holles Street

No. of Irish Universities hosting NCRC supported research

7

- National University of Ireland, Galway
- National University of Ireland, Maynooth
- The Royal College of Surgeons in Ireland
- Trinity College Dublin
- University College Cork
- University College Dublin
- University of Limerick

No. of research professionals supported

165

- 98 Principal Investigators (PI or Co-PI)
- 20 Postdoctoral researchers
- 12 Research Assistants
- 13 Clinical Research Fellows

Clinical research Studies Supported Across Irish Paediatric Hospitals by the CCRU

47

- 26 Clinical Trials of IMP/Medical Device Investigations
- 21 Non-Interventional Studies
- 10 Therapeutic Areas

No. of countries collaborating on publications

1068

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I am pleased to report that during 2018, the National Children’s Research Centre expanded its support for internationally competitive, high quality research that improves the health of children. We are extremely grateful to the Children’s Medical Research Foundation whose fundraising efforts make our support for paediatric research possible.

The Board of NCRC was very much aware of the historic changes taking place during the year in paediatric services and their implications for research and the future role of the NCRC. On 1st January 2018, Children’s Health Ireland was established, merging Our Lady’s Children’s Hospital, the Children’s University Hospital Temple St and children’s services at Tallaght Hospital.

Building of the new Children’s Hospital advanced rapidly in Dublin 8 as did the building of the satellite centres in Blanchardstown and Tallaght. Additionally, the Children’s Health Foundation was established, merging the experience and expertise of the Children’s Medical Research Foundation and the Temple St Foundation in raising funding for paediatric research and the improvement of children’s services. Work also began on defining the involvement of the academic institutions with a responsibility for educating paediatric clinicians and conducting paediatric research with Children’s Health Ireland.

Against the background of these changes, the NCRC formulated its view about how best to support the ambition of Children’s Health Ireland to be a research intensive, world class hospital for children. With over 50 years of experience in supporting and providing an infrastructure for paediatric research, in close association with academic and hospital partners, the NCRC has a unique expertise to bring to support the mission of the new Children’s Hospital.

NCRC proposed that it continue to carry out its mission by being the research pillar of the academic partners involved with Children’s Health Ireland, a proposal that was broadly welcomed.

I would like to thank our Chief Executive, Dr Jacinta Kelly, for her strategic leadership of the NCRC in a complex and changing environment and for her commitment to paediatric research. I would also like to acknowledge the skill and professionalism of all the staff of NCRC.

Finally, I am most grateful to my fellow directors for their commitment to and support for the mission of the NCRC.
Building capacity in paediatric research in Ireland has never been more important, as progress is made in the development of the new National Children’s Hospital in Dublin 8.

Huge progress has been made this year in bringing together the three Dublin Children’s Hospitals into one entity, Children’s Health Ireland (CHI) and also the creation of Children’s Health Foundation (CHF) from a merger of our long time funders CMRF, with Temple St Foundation. We are very grateful that this new Foundation continues to support NCRC in enabling paediatric research through its activities, reflected in this report.

Building on the success of last year, the NCRC has continued to grow high quality paediatric research. Through the awarding of competitive, high quality and progressive research grants, provision of a research laboratory and biosample storage facility, and support for the conduct of clinical trials through the Children’s Clinical Research Unit, NCRC has continued driving progress in paediatric research.

The period of April 2018-March 2019 has seen our number of active grants increase from 43 to 61. The range of active grants ensure a wide range of researchers, including scientists, nurses and allied health professionals, clinical Consultants and Professors are supported in conducting research with real impact on child health. NCRC is unique in the range of grants that it provides across the research spectrum, and we have developed this in order to foster a research-active community across the paediatric healthcare professions.

It is not possible to include details here of all the exciting projects funded by the NCRC, and this year we have focussed our Highlights Report on our priority areas of Childhood Cancer, Vascular Biology/Cardiology and Immunity and Infection. We have chosen some of the projects within these fields to give a sense of scale and scope of the work ongoing in these areas of huge significance to child health. The full spectrum of research is represented from cutting edge molecular technology, to engaging whole families in coping with a diagnosis of childhood cancer.

However, one theme emerges strongly from the research reports this year, and that is how research is driving personalised medicine in paediatrics.

Technology now allows researchers to analyse the individual patient at the molecular level and allow their unique makeup to influence the development of treatments. This approach will lead to more targeted therapies, improved survival and will diminish toxic side effects of treatments; as with all good research, it will become part of routine diagnostics in the future. This development highlights the need for the existence of translational research facilities, such as provided by the NCRC’s laboratory and funding portfolio, in the paediatric setting.

Finally our CCRU, supporting the conduct of clinical trials in children by Hospital Consultants, has continued its vital work to ensure that Irish children have access to international clinical trials. The future of this Unit lies within CHI and NCRC is working with CHI to ensure this happens in the short term.

Once again we would like to thank our funders CHF, and their generous donors, for their continued support. We look forward to continuing to work with them, and with CHI, in the drive to ensure that the paediatric research community is ready for the new Hospital and the unrivalled opportunity it presents to have a world class, research-active Children’s Hospital in Ireland.
Introduction to the NCRC

Who we are:
Established to improve the lives and health of children through research, for over 50 years the National Children’s Research Centre (NCRC) has been at the heart of paediatric research in Ireland.

Based on the grounds of Children’s Health Ireland (CHI) at Crumlin, formerly Our Lady’s Children’s Hospital, Crumlin, the NCRC is the largest paediatric research centre in the country. The purpose of the NCRC is to enable, grow and sustain a paediatric research community in Ireland and we do this by providing a framework of supports around which research and researchers can flourish. Through our competitive research grants, state of the art laboratory, and Children’s Clinical Research Unit, we facilitate the conduct of high-quality research by academic researchers, clinicians, nurses and allied health care professionals working in paediatrics.

Our Vision:
To be the National Centre for paediatric research and research education in Ireland, and to be recognised nationally and internationally for the quality of our research, our contribution to the advancement of paediatric medicine, and as a driver of the global paediatric research agenda.

Our Mission:
To support internationally competitive, high quality research that has a real and lasting impact on child health.

50 years
At the heart of paediatric research in Ireland
What we do:

The type of research we support:
From clinical questions asked at the patient’s bedside, to the laboratory bench where we seek answers at the cellular and molecular level, to supporting clinical trials, we support the full spectrum of basic, translational and clinical research.

Who we support to conduct this research:
Researchers at all stages from postgraduate students to Professors. We encourage a multidisciplinary approach across academic researchers, clinicians, nurses and allied health care professionals and provide a range of grants to support the whole research community. With Ireland now set to welcome a new National Children’s Hospital where the majority of the paediatric population with significant illness will be seen at a single site, creating a population of paediatric research professionals is important now more than ever.

How we support them:
Research Grants: The NCRC has been building paediatric research capacity in Ireland for over 50 years through a range of competitive grants. These have evolved over the years in an effort to meet the needs of the whole research community. Starting with small grants to cover postgraduate fees and seed funding to support start-up projects, they progress to full fellowships for clinicians, nurses and allied health professionals. Our project grants offer substantive support across the entire spectrum of translational research and allow for funding of postgraduate and postdoctoral researchers under the guidance of senior research personnel who direct the project. We are also aware, as we move towards the New Children’s Hospital, of the need to support senior professionals and research leaders. The NCRC Research Leadership Award has been initiated to facilitate the creation of leadership roles in key areas of paediatric research to ensure it is embedded at senior levels across the hospital and academic institutes.

Children’s Clinical Research Unit (CCRU): This unit provides highly trained specialists in clinical research to support clinical trials and studies, which are essential in addressing unanswered medical questions and clinical challenges. The support, expertise, and physical infrastructure provided by the CCRU means that studies specifically tailored for children can be carried out by Consultants and their teams across Irish paediatric hospitals. Clinical research is developed after years of evidence is provided from basic and translational research, and in turn, clinical studies link back to the scientists at the bench, providing patient samples and data that allow us to examine the very basis of disease, as well as its diagnosis and treatment, in order to improve the outcome of childhood disease.

Laboratory Facilities: Having a laboratory on the grounds of CHI at Crumlin has been a key enabler of research within the Hospital, and its partner universities, for over 50 years. The location, in close proximity to the largest children’s hospital in the country, is vital, as it allows paediatric scientists, doctors, nurses, and allied health professionals have access to a state-of-the-art research facility. The Laboratory also houses a biosample storage facility which is vital for the secure storage of precious patient samples. These samples are obtained only after the research has been deemed ethical, and consent has been obtained.
Introduction to the NCRC
In order to build and sustain a lasting paediatric research community, we must invest in the continuum of research from the laboratory bench to the patient’s bedside. To encourage lasting growth, it is important that this investment starts with education and training to prepare our future research professionals. It must also provide a framework to allow active researchers to grow their work, while acknowledging the importance of leadership and our most senior professionals.

Within the field of paediatrics there is a wide array of research topics. We endeavour to maintain support for key areas already well established in Ireland, while injecting investment into newer and more undeveloped areas. This is reflected in our strategy with the prioritisation of specific research areas in child health.

These are: Immunity and Infection including Cystic Fibrosis, Childhood Obesity, Dermatology, Gastroenterology, Down Syndrome and Rheumatology; Childhood Cancer; Cardiology and Vascular Biology. Emergency Medicine; Orthopaedics; Neurology and Neonatology are ‘pipeline’ areas of research.

The NCRC offer substantive support through a range of competitive funding schemes, all of which are assessed and reviewed in accordance with international best practice to ensure quality.

The cornerstone of this process, which is managed by the NCRC, is International Peer Review. In essence, this involves each eligible application being assessed by a bespoke panel of international reviewers, selected because of their expertise in the field.

A minimum of three reviewers are required per application, and in order to proceed for consideration by the NCRC Scientific Advisory Committee, they must receive an average score of 70%. This guarantees that we fund only the highest quality of research, that is both novel and with real potential to impact child health.
NCRC Funding Schemes

Co-Funded Research Partnerships

The NCRC currently co-fund 4 PhD research partnerships with the Irish Research Council (IRC) as part of their Enterprise Partnership Scheme (Postgraduate). This is a national initiative designed to link excellent early-career researchers with enterprise. The scheme co-funds researchers who dedicate their time to a specific research project related to the mission of the NCRC. The aim of this award is not only to achieve a post graduate degree, but to have gained experience from an enterprise that is not traditionally included in postgraduate training. This is a competitive process, managed according to international best practice that is in keeping with the NCRC’s own awarding methods.

NCRC Research Education Support Grant

The NCRC Research Education Support Grant covers the cost of university registration fees for hospital staff wishing to undertake a postgraduate degree by research. This award came about because of the rising number of clinically active professionals wishing to undertake research, but unable to step away from their clinical roles. This award allows individuals to maintain their clinical posts while conducting research, with the support of their department head.

It is aimed at clinicians, nurses and allied health professionals working in a paediatric hospital environment.

Supports:
- PhD students
Value:
- €32k max over 4 years

NCRC Innovation

Designed specifically to foster innovative ideas, build new partnerships, and support novel research, the NCRC Innovation Award provides a start-up fund to allow researchers the time and resources to gather data to support a more substantial project application in the future. The aim of this initiative is to develop new avenues of research and foster the growth of new research projects and professionals.

Supports:
- Academic or clinical researchers who are postdoctoral or equivalent
Value:
- €50K max over 1 years

Supports:
- Clinical, nursing and allied health care professionals conducting a research MSc, MD or PhD in a paediatric hospital environment.
Value:
- €24k max over 3 years (fees only)
NCRC Clinical Research Fellowship

The NCRC Clinical Research Fellowship was developed specifically to train the clinical researchers of tomorrow, as we believe that research should be part of clinical care. The aim of the Clinical Research Fellowship is to support suitably qualified MD, PhD and MSc candidates to pursue research, full- or part-time, in the field of paediatric medicine. The Clinical Research Fellowship is aimed at clinicians, nurses and allied health professionals working in paediatrics.

Supports:
Clinical, nursing and allied health care professionals conducting a research MSc, MD or PhD

Value:
€270k max over 3 years

NCRC Paediatric Research Project Grant

NCRC Paediatric Research Project Grants are intended to consolidate and grow high quality research that would have a positive, long-term impact on child health. This award supports the entire spectrum of translational research, allowing us to harness knowledge gained from basic research to bring new drugs, devices and treatment options to the patient. This award fosters truly multidisciplinary alliances across paediatric hospitals and higher education institutes by bringing together academic scientists, clinicians, nurses and allied health professionals.

Supports:
Senior academic and clinical researchers who may hire research assistants, postgraduate students or postdoctoral researchers through the award

Value:
€300K max over 3 years

NCRC Leadership Award

Across a range of funding schemes designed to support research and research professionals at every level, the NCRC has been building paediatric research capacity in Ireland for over 50 years. With Ireland now set to welcome a new National Children’s Hospital where most of the paediatric population will be seen at a single site, creating a population of paediatric research professionals is important now more than ever. As we move towards a hospital of this magnitude, we must also consider the need for support of senior professionals and research leaders. The NCRC Research Leadership Award has been initiated to facilitate the creation of leadership roles in key areas of paediatric research. This award will ensure paediatric research is embedded at senior levels across our academic institutes. This combined with our other funding initiatives provides a framework upon which paediatric research professional can build their experience and aspire to senior positions within Ireland, while at the same time attracting international experts and raising the profile of paediatric research in Ireland.

Supports:
Senior academic and clinical research personnel

Value:
€300K max over 3 years plus a salary contribution commensurate with academic entry level and in agreement with host institute salary scales, for an approved period
NCRC supports paediatric research from bench to bedside and across a multi-disciplinary research community. From postgraduate students to senior academic and clinical personnel, we are working to grow the paediatric research community in Ireland.
Growing a childhood cancer research community in Ireland

Because of the relentless work internationally of clinicians, nurses, allied health care professionals and scientists, the survival rate for childhood cancer is now ~80%, a striking increase from rates of ~10% that existed only 40 years ago.

Ideally placed on campus in CHI at Crumlin, the centre for childhood cancer in Ireland, the NCRC has for many years been working to bring clinical and research professionals together to support the fight against childhood cancer.

The NCRC believe that despite this dramatic improvement, we need to do more. More for the 2 in 10 children who will not survive a cancer diagnosis. More for children with neuroblastoma and brain tumours whose outcomes remain poor. More for the 6 in 10 survivors who develop long term side-effects, often due to the treatment itself. Only through research will it be possible to improve these outcomes and ensure that children not only survive but thrive after a cancer diagnosis.

During the reporting period, we supported researchers at all levels from postgraduate students awarded Research Education Support Grants, to clinicians and scientists embarking on pilot studies through the Innovation Award, to more senior research professionals awarded Paediatric Research Project Grants, and support of leaders in the field with the Brendan McGonnell UCD Professor of Paediatric Molecular Haemo-oncology. These projects all demonstrate a collaboration between academic researchers and clinically active healthcare professionals. The breadth of cancer research supported by the NCRC is reflected in the projects supported during this period. These span basic research to better understand the underlying genetic factors influencing neuroblastoma and clear cell sarcoma of the kidney, to design of more targeted, personalised treatment to improve treatment of brain tumours, neuroblastoma and certain leukaemias, to the psycho social impact of a childhood cancer diagnosis and end of life care.
Improving the treatment of childhood leukaemia

The greatest success in childhood cancer has been in blood cancers, specifically leukaemia, where the most significant improvement in survival has been made. However, current therapies don’t work for everyone. Relapses occur and remain difficult to treat; treatment side-effects can be severe, and many survivors must cope with a reduction in quality of life, especially for adolescents and young adults. To improve this situation, we must first understand why this is the case. This is exactly what Professor Jonathan Bond is working to achieve.

Under the NCRC Research Leadership Award Scheme, Jonathan took up the post of Brendan McGonnell Professor of Paediatric Molecular Haemo-oncology Chair in UCD in early 2018. With this post Jonathan was also awarded a research grant to allow him set up a research team to better understand more difficult to treat blood cancers using computational analysis of the many factors that influence cause, progression and response to treatment.

This year, his group have focused on the development of blood cancer ‘models’ that can be examined in the lab. These are known as cell line models. To create these, cancer cells from a donor are grown in an artificial environment which allows scientists to examine the behaviour of the specific cancer. It allows them to examine the effects of new treatment, and to discover how cells can resist treatment by identifying the complex collection of genes and proteins involved. In parallel, his team are designing computer models to analyse this complex network of genes and proteins. Using this technique, they hope to identify areas that are vulnerable to new treatments, which will result in more precise and effective targeted treatments for children with blood cancers, greatly improving their recovery and overall quality of life.

80%

The survival rate for childhood cancer is now ~80%. Work is ongoing to improve outcomes for the 2 in 10 children who do not survive a cancer diagnosis.
Bone marrow transplant: Predicting immune response

Understanding the cause of treatment failure is also the focus of the work being carried out by Dr Günther Eissner, University College Dublin (UCD) and Professor Owen Smith (UCD and CHI at Crumlin), who are investigating how to reduce complications after bone marrow transplant, the only curative option for certain types of leukaemia.

A bone marrow transplant, also called a stem cell transplant, is a procedure performed to replace bone marrow that has been damaged or destroyed by disease, infection, or chemotherapy. This procedure involves transplanting blood stem cells from a donor that travel to the bone marrow of the recipient, where they produce new blood cells and promote growth of new marrow.

3 in every 4 paediatric patients survive bone marrow transplant, but for the 1 in 4 who do not survive, damage to the lining of blood vessels, also known as endothelial damage, is a significant issue. We know that this damage is caused by white blood cells from the donor that specifically attack the lining of blood vessels of the recipients: what is not known is how to distinguish patient/donor pairs that are at high or low risk of this damage occurring.

Similar to the work being conducted by Professor Bond, this group are also using cell line models to understand this process. Using special laboratory techniques, they are growing donor cells with cell line models generated in the laboratory, in order to assess the risk of damage to the lining of blood vessels for individual patient/donor pairs. These experiments will be used to identify which patient/donor pairs are most likely to suffer severe endothelial damage. Based on this information, high risk patient/donor pairs can be prescribed a prophylactic drug regimen to protect the recipient them during the transplant period. Better classification of patients and donors before transplantation will also mean that low risk patient/donor pairs could be transplanted without the need for the same drug regimen.

The ground-breaking project is still in the proof-of-concept phase but will move to using patient samples soon. Patient samples are precious, and it is therefore imperative to optimise the process of maintaining these cells in the laboratory, and the techniques for testing the patient/donor response, before patient samples are used.

As better techniques are being developed for bone marrow transplantation, nearly every patient will have a potentially suitable donor in the future, thus the number of transplants is likely to increase. A better understanding of the complications caused by damage to the lining of blood vessels, along with more effective use of available treatments, should decrease this figure and may have a profound life-saving impact for children undergoing this procedure.

Award:
Paediatric Research Project Grant

Team Leaders:
Dr Günther Eissner and Professor Owen Smith

Research Team:
Isabel Arias Quiró (Research Assistant), Simeng Li (PhD Student)
Developing Personalised Treatment for Children with Brain Tumours

Brain tumours are the most common cancer in children aged 0-14 years, and of these, the most common form is medulloblastoma, accounting for 2 in 10 paediatric brain tumours. Every year, approximately 500 children are diagnosed in the US, and 10 in Ireland. All patients are treated aggressively with surgery, radiation therapy and chemotherapy and while survival rates have improved, many children are left with long-term disability because the treatment also affects their still-developing brain. As a result, survivors may experience developmental delays and fertility issues due to hormone imbalances, poor mobility, delayed speech, poorer cognition, and tend not to do as well as their peers in school. To spare patients the toxic side effects of treatments that may hold no benefit for them, in particular the use of radiation therapy, it is vital that we find ways to predict how individual patients will respond to both currently available and new drugs, so that the most suitable treatment can be given to each patient. This need forms the basis of the research being led by Dr Brona Murphy, Mr Darach Crimmins and Mr Phillip O’Halloran, in a collaboration between the Royal College of Surgeons, Beaumont Hospital and CHI at Temple Street. Using a computer program called ‘APOPTO-CELL’ which has been shown to be useful in adult brain tumours as well as colorectal cancer, they have shown that measuring the amounts of 5 proteins that are involved in cell death might be able to predict how some tumours will respond to standard chemotherapy.

Cancer cells can contain a number of different proteins that make them resistant to commonly used chemotherapies. Recently, new drugs have been developed that specifically target and neutralise these proteins, but identifying which drug is best for each patient is a challenge. Using a technique called ‘BH3 profiling’, they have shown that some medulloblastoma cells are dependent on a protein called Bcl-xL to make them resistant to chemotherapy. Using this information, Brona’s team used a drug that specifically neutralises Bcl-xL along with standard chemotherapy and found that the combination of these drugs was much more effective at killing cancer cells than either drug alone. This result showed that BH3 profiling has the potential to predict which protein should be targeted to kill cancer cells most effectively.

Ultimately, this work will contribute to the development of clinically relevant tools that are capable of identifying the most effective treatment combinations for the individual. In the long term, this work has potential to create a decision-making tool for use in the clinic that can facilitate personalised treatment in specific patient groups, allowing the reduction or elimination of radiation therapy, and ultimately reducing long-term side effects and disability.
What fuels Natural Killer cells in neuroblastoma patients?

Neuroblastoma is the most common extra-cranial solid tumour in children. It accounts for approximately 5% of all childhood cancer but is responsible for 15% of childhood cancer deaths. It is one of the most challenging cancers of childhood. Patients with high risk neuroblastoma have a five-year survival of just 40-50%, which means for every 10 children with high-risk neuroblastoma, 4 to 5 will be alive 5 years after diagnosis. It is urgent therefore, that we improve this survival rate and to do so we must develop new, innovative therapies for children with neuroblastoma.

A breakthrough in treating some cancers has been the development of antibody-mediated immunotherapy. This treatment works by coating cancer cells with an antibody the immune system can recognise. By doing this, it directs the patient’s own immune system to kill the cancer cells. The main cell of the immune system that carries out this task is aptly called a Natural Killer (NK) cell. In neuroblastoma, anti-GD2 therapy works by increasing the amount of tumour cells that NK cells can kill. The introduction of anti-GD2 immunotherapy improved two-year event free survival from 46% to 66% compared to standard therapy, but the treatment is not effective in everyone and it can have severe side effects. Therefore, there is an urgent requirement for new and better treatments that improve the overall survival rates but also have less impact on patient quality of life.

There is evidence that NK cells in neuroblastoma patients do not work properly, a fact that would reduce the efficiency of immune therapy given to patients. Research being conducted by Professor Clair Gardner and Dr Cormac Owens in a collaboration between Trinity College Dublin and CHI at Crumlin, is looking at how neuroblastoma impacts the immune system. Clair’s team have shown that the way in which normal NK cells metabolise their fuels impacts upon their functions. This project is investigating how NK cells from neuroblastoma patients metabolise their fuels, and whether this is different to NK cells from healthy children. If it is, they will explore ways in which they can target this altered metabolism in order to increase the anti-cancer functions of NK cells in neuroblastoma. By studying the immune system of 3 patients with neuroblastoma diagnosed between 2018 - 2019, they are beginning to understand how and why the immune system of patients is different. Ultimately, the aim is to discover new future therapies that target the immune system and can be rapidly translated into clinical practice for the benefit of vulnerable patients.
Cancer

Childhood cancers
Bringing the whole family into focus

The last 50 years have seen significant advances in the treatment of childhood cancers. This is reflected in overall childhood cancer survival rates which have risen from 10% to ~80% during this time. The quality of life of those living with and beyond cancer has always been a concern. The life-threatening nature of the illness during childhood, the intensity and unpredictability of treatments as well as its visible effects, reach beyond the patient to the whole family and significantly elevates the level of distress for all involved. Throughout treatment and recovery, the whole family faces many challenges. Changes to family life, broken routines and uncertainty regarding the prognosis of the child with cancer can push parental resources to the limit. As a result, the needs of siblings can sometimes be overlooked or side-lined. Research to date has mainly focused on the experiences of children with cancer and their parents, with few studies focused on or including siblings. Recognising the need for parental and sibling support, a partnership was born between Haematology/Oncology and Psychology Department at CHI at Crumlin. This research collaboration aims to develop a service to support adjustment of the whole family to cancer diagnosis and treatment and is being led by Professor Owen Smith, Consultant Paediatric Haematologist CHI at Crumlin and Professor of Paediatric & Adolescent Medicine (UCD), Dr Jane Pears, Consultant Oncologist, CHI at Crumlin and Dr Chiara Besani, Senior Clinical Psychologist Psycho-oncology Department, CHI at Crumlin.

Chiara is an expert in this field, having developed the pilot study of the current therapeutic intervention as part of her PhD in Queen’s University, Belfast. It involves a 1-day workshop to foster resilience, coping, family communication and family functioning with parents and siblings. Participants complete different activities to help them to express their questions, worries, fears and emotions about medical and psychological aspects of their brother/sister’s cancer diagnosis. Participants also take part in activities that help them to learn different ways to find solutions for difficult problems and situations. The NCRC recognise that the first step in developing any service is to conduct clinical research to inform how effective an intervention can be. It is hoped that the initial investment made in this area through the NCRC Innovation Award will lead to a more extensive study and help to build research capacity in Paediatric Psycho-oncology, an area of clinical research that is still in infancy.
When cure is no longer an option in Paediatric Oncology Care

Overall, 2 in 10 children will not survive a cancer diagnosis. For the parents of these children it is essential psychosocial support needs at end of life and following immediately the death of a child are accurately identified. To do this, it is important to examine bereaved parents’ perspective on the end of life care period, end of life conversations and their bereavement support experience immediately after and following the death of a child. These findings should then be incorporated into new practice.

Kim Murray is a Social Worker in the Haematology Oncology department of CHI at Crumlin. Supervised by Dr Stephanie Holt (TCD), Dr Cormac Owens (CHI at Crumlin and UCD) and Dr Gloria Kirwan (NUI Maynooth) she is conducting research to identify the support needs of parents at end of life and following the death of a child. The overall aim of this work is to reduce parental suffering and psychological symptoms such as anxiety and long-term distress following bereavement.

The body of literature regarding end of life care and support services following the death of a child identifies the need for further research to establish the needs of parents to prevent prolonged anxiety and suffering. In 2017 research conducted by Trinity College Dublin reviewed over 500 articles published on the psychosocial support needs of parents and families in an oncology setting. The social support needs for parents during the stages of diagnosis, treatment and remission was well documented, however the need for further research was highlighted in relation to end of life care and the social support needs of bereaved parents.

The design of the study will incorporate both the psychological impact and the impact of family beliefs, family legacies, ethnicity, religious beliefs and societal values and practices on parents’ response to grief and loss. The findings will provide rich material to inform best practice for healthcare professionals during end of life conversations and reduce parental suffering during end of life care and following the death of a child.
Vascular Biology & Cardiology

Research Highlights

Building capacity in vascular biology and cardiology, key NCRC research priority areas

One in 100 children in Ireland is born with a structural defect of the heart. New techniques have resulted in improved survival rates for children with complex cardiac conditions, and research in this field continues to push the boundaries to ensure that these children survive and thrive. All paediatric surgical and cardiac catheterisation cases for the island of Ireland are now performed at the Children’s Heart Centre in CHI at Crumlin, in line with the development of an all island congenital heart disease service. Based alongside the main hospital at CHI at Crumlin, the NCRC is perfectly placed to be central to this research.

The related field of Vascular Biology examines haemostasis, thrombosis, platelet biology, vascular inflammation and blood vessel development. Because many childhood diseases have a vascular dimension to them, the NCRC has in recent years included Cardiology and Vascular Biology as a joint research priority area.

Research underway in Cardiology and Vascular Biology includes blood vessel blockade and childhood malaria; developing living, growing heart valve devices for children of families affected by a sudden cardiac death; creating human cell line models to examine salt imbalance in heart cells and using genetic sequencing to understand predisposition in children with Kawasaki Disease.
Malaria is an infectious disease caused by Plasmodium parasites, typically transmitted through the bites of female Anopheles mosquitoes. Malaria is endemic in 107 countries in tropical and subtropical regions. The global morbidity and mortality caused by malaria infection are staggering, with between 300 million and 500 million cases of clinical malaria occurring each year. Malaria results in more than 500,000 deaths every year, approximately 80% of which occur in African children under the age of five, making malaria one of the leading causes of death in young children worldwide.

Following a bite from an infected mosquito, parasites are released into the bloodstream. The parasites travel to the liver where they mature and multiply and are subsequently released back into the bloodstream where they infect, multiply within, and destroy red blood cells. This process leads to symptoms such as fever, chills, headaches, nausea and vomiting, muscle pain and fatigue. However, in severe cases of malaria infection, a life-threatening neurological complication called cerebral malaria (CM) can develop.

Young children with CM typically present to hospital with severe headache and drowsiness. Unfortunately, as the malaria infection worsens, the children rapidly progress to develop confusion, decreased consciousness and unrousable coma.

Although effective anti-malarial drugs have been developed, in up to 20% of children CM still proves fatal. Furthermore, 20% of the children who survive CM are left with long term complications including learning difficulties and memory impairment.

In spite of the significant mortality and morbidity associated with CM, the effects of the malaria parasite in causing disease remain poorly understood. This lack of understanding has impeded the development of new and much needed treatment options for children who develop CM. In a collaboration between RCSI, TCD, Liverpool School of Tropical Medicine and CHI at Crumlin, collectively known as the NCRC Malaria Research Consortium, Prof James O’Donnell, Prof Owen Smith, Prof Alister Craig and Prof Matthew Campbell are leading research into the biology underlying CM in children. Previously, the Consortium has identified a novel role for a specific blood clotting protein called von Willebrand factor (VWF) in malaria. In the blood, this clotting protein is able to bind to red cells infected with malaria parasites. In recent work supported by the NCRC, the Consortium is investigating further how VWF influences malaria progression.

Ultimately, the aim is that understanding how VWF is important in children with malaria infection may provide new treatment options, with global impact.
Research Highlights

Vascular Biology & Cardiology

Living, Growing Heart Valve Devices for Children

Every year, an estimated 300,000 patients worldwide require surgical replacement of diseased or dysfunctional heart valves with a prosthetic valve, and this number is estimated to triple by 2050. A significant number of new-borns (approximately 1 in every 100 live births) are affected by congenital heart disease, the most common of which affects the valves, contributing to 44,000 cases annually. Around 650 children in Ireland are born with structural abnormalities of heart every year, many of whom require surgical reconstruction and an artificial heart valve implantation.

Current heart valve replacement options for children are limited by their inability to grow and remodel, requiring numerous invasive surgeries to implant larger valves as the child’s heart outgrows the implant. Tissue engineering aims to repair damaged and defective organs by combining cells from the patient with temporary degradable biomaterials that guide the growth of new tissue.

Research being led by Dr Tom Flanagan (UCD) in close collaboration with Prof. Damien Kenny (CHI at Crumlin) and Prof. Massimo Caputo (University of Bristol) aims to target the unmet clinical need for a biodegradable, stented valve in children that promotes tissue healing resulting in living valve tissue that will grow as the child’s surrounding heart grows. The ultimate goal is to reduce, or indeed remove the need for successive valve implantation procedures in children (due to outgrowth of an implant) and to apply the same technology to adults (due to failure of current, non-viable prostheses with a limited life-span).

Tom is working on developing a novel tissue-engineered heart valve by mimicking the normal valve structure of the heart using a simple tube-in-tube approach which will encourage tissue regeneration at the implantation site. Tom has been working in this field for the last 15 years, and over that time has gathered extensive information on the composition of valve tissue and how cells behave in and repair the valve, which provides a blueprint for artificial valve devices, and has allowed the team to refine the structure and materials needed for a living, growing valve with potential for keyhole implantation in children.

The proposed valve will be deliverable to the child’s heart on a novel biodegradable 3-D printed stent through keyhole surgery. It is anticipated that this study will form a substantial basis for the use of minimally-invasive devices in the treatment of heart valve defects in children. This has the potential to change the landscape of paediatric valve intervention procedures, by reducing morbidity, the number of risky surgical procedures and consequently, overall healthcare costs.

Award:
Paediatric Research Project Grant

Project Grant:
Team Leaders: Dr Tom Flanagan, Prof. Damien Kenny and Prof. Massimo Caputo

Research Team:
Dr Douglas Ramos Marques (Postdoctoral Researcher), Ana Le Chevillier (PhD Student)
Creating human cell line models to examine salt imbalance in heart cells

A significant burden of human illness is attributable to malfunctioning ‘pores’ on the surface of cells in the brain and the heart. The flow of salts into and out of the cells through these pores happens multiple times a second with each heart beat and brain impulse. When these malfunctioning pores do not allow the salts to flow as intended, it places the person at risk of the heart arresting (from a dangerous rhythm) or from a convulsive seizure.

Oftentimes the DNA code for the malfunctioning pore has a single isolated ‘spelling mistake’ but if the error is in a critical region of the pore, it interferes with the salt balance within and outside the cell. Salts carry an electrical charge. A delay in the flow can interfere with the ability of the heart or brain cell to accept an electrical signal from a neighbouring cell. Much like a so-called ‘Mexican wave’ at a football stadium, if some participants are late in reacting to those around them, it looks uncoordinated; in the case of the brain or heart, it can set up regions of electrical instability in the brain or heart. This translates to a potential electrical short-circuit manifesting as a epilepsy or in the heart arresting.

Research led by Dr Terry Prendville (CHI at Crumlin) and Prof. Nicholas Allen (NUI Galway) is providing information about this process by examining cells from families that appear to pass the trait from one generation to the next. Recent technological advances enable scientists to turn skin cells from such family members into heart or brain cells alive in a dish. This is done by first rewinding the biological clock of the skin cell and ‘re-programming’ it to be embryonic stem cell-like cell, which then have the potential to become any cell in the body. Essentially, this research is coaxing the stem cell to become either a 100-day firing brain cell or a beating heart cell to allow the researchers study disease pathologies.

The second major technological advance this project ambitiously aims to harness is the ability to ‘correct’ the genetic mistake and to potentially ‘repair’ the epilepsy or cardiac rhythm disorder in these cells – still in a dish. Although this DNA repair has not been attempted inside a living person’s own body, many diseases may in the future be treated, prevented or cured using DNA repair technology and this project supports the development of this revolutionary advance. This project will demonstrate if gene correction in the lab can rescue salt imbalance in patient brain or heart cells and importantly, provide human cell models for novel drug screening.
Kawasaki disease (KD) is a disease that causes inflammation of blood vessel walls. It is the most common acquired cardiac condition in childhood in the developed world. Up to a quarter of untreated children affected by the disease develop coronary artery aneurysms (CAAs). CAAs are dilatations of the blood vessel wall. This can lead to scarring of the wall, clot forming in the blood vessel, a decreased blood supply to the heart and damage to the heart muscle tissue. Patients require life-long follow up and life-long medical treatment in the form of ‘blood thinners’.

Although the underlying cause of KD is unknown, it is thought to have a genetic basis. This is due to the fact that it is seen more commonly in people of a certain ethnicity (for example Japanese people), even if they have grown up in a different country (for example USA) meaning that the increased incidence of KD in Japanese people does not appear to be solely due to environmental conditions.

New research being carried out by Dr Sarah Doyle (TCD) and Prof. Colin McMahon (CHI at Crumlin) plans to analyse the genetics of 2 groups of patients with KD: those who develop coronary artery aneurysms and those who do not. The objective is to identify genetic mutations in the first group which they think cause an increased risk of developing CAAs.

Genetic material will be extracted from blood samples and used in a technique called whole exome sequencing.

This is a way of looking at the DNA that is responsible for coding proteins (the building blocks of the cell) but not looking at the other parts of the DNA. This means analysis of the DNA is easier and quicker to perform. It also means there is less data to store and it is a relatively inexpensive method of analysing genes.

By using whole exome sequencing in an Irish KD population, the team hope to identify slight differences or ‘mutations’ in the DNA that are associated with an increased risk of development of coronary artery aneurysm formation in patients with KD. These are likely to be found in genes with immune-related functions or in genes that control the maintenance of the blood vessel wall.

Findings of this study have the potential to advance the understanding of the how and why coronary artery lesions form in children with KD. In this way, targets for new treatment options could be identified. Significantly, this work may also lead to earlier identification of children who are at higher risk for coronary artery lesions compared to those who are not. Children who are high risk can then be treated more aggressively from early on in their disease course, to prevent CAA.

It is hoped that a combination of earlier identification of high-risk individuals and potential new treatment targets could lead to an improved overall prognosis.
Continued support for the paediatric research community, who are working to solve problems in Immunity & Infection

Immunological responses are the basis of almost all disease pathology, and globally the study of immunity and infection is at the cutting edge of medical research. Advances in this field have shaped contemporary healthcare, including vaccination and cancer immunotherapy.

Ireland ranks among the top 3 countries in the world in the field of Immunology, and Immunity and Infection has been a key priority area for the NCRC for many years. Not surprisingly NCRC supported researchers have built a considerable reputation in this field and we are proud to consistently attract research leaders who continue to push the boundaries of our understanding of childhood disease across a number of areas.

Areas currently supported through NCRC grants include the lung damage in cystic fibrosis; childhood allergy; rheumatological diseases; Down Syndrome; and vaccine design and development. Diseases with global impact, such gastrointestinal infection, childhood obesity and inflammatory bowel disease are also studied within this focus area. The NCRC also house two longitudinal clinical studies – SHIELD CF for cystic fibrosis and DOCHAS for childhood IBD, which are ensuring that new discoveries in these fields will be made now and into the future.

Because of its fundamental importance to disease development, Immunity and Infection is currently the largest area supported by the NCRC and spans all of our funding schemes. Highlights of the current reporting period are outlined here and include better understanding of sepsis in newborns; why newborns have increased risk of tuberculosis; investigating if changes in the immune system caused by obesity are making it more difficult to treat children with Type 1 diabetes and understanding the differences in the immune system in babies with brain injury.
UNICORN: Underlying mechanisms in Neonatal Immune Metabolic Dysregulation and Brain Injury

Even after an apparently normal pregnancy and delivery, some babies display symptoms of a brain injury including seizures, respiratory problems, and loss of consciousness. This brain injury can lead to devastating long-term consequences including developmental problems, cerebral palsy and death. While technological advances in brain imaging have helped to diagnose babies with brain injuries, strategies to effectively prevent and treat the brain injury are still lacking. Cooling therapy is the only treatment available, but 50% of affected infants still have poor outcomes.

In babies with a brain injury, increased systemic inflammation has been associated with more severe developmental problems. Research from Prof. Eleanor Molloy’s group in TCD has demonstrated that certain immune cells called neutrophils and monocytes are over activated in babies with evidence of a brain injury.

Building on Prof. Molloy’s work, and supervised also by Dr Fionnuala Hickey, Clinical Research Fellow Dr Mary Isabel O’Dea (TCD) aimed to increase our understanding of the changes seen in the immune system of babies with a brain injury in a collaboration with CHI at Crumlin, the Coombe Women & Infants University Hospital and CHI at Tallaght. Mary compared the immune cell function in babies with evidence of a brain injury to normal healthy controls and assessed if the differences observed were related to the severity of the brain injury.

Her work has resulted in the identification of potential biomarkers that could be used to predict the babies at the greatest risk of developing long term neurodevelopmental problems. By understanding the differences in the immune system in babies with brain injury in comparison to healthy controls, she hopes to develop new treatment strategies to reduce brain injury.

50% of infants affected by brain injury do not respond well to available treatments.
Tuberculosis (TB), caused by the bacteria *Mycobacterium tuberculosis* (MTB) is the single biggest infectious killer in the world and a leading cause of child death worldwide. Worldwide every year, at least one million children will be diagnosed with TB, and of those infected, over a quarter of a million children will die. Newborn babies are at greatest risk of developing TB. We know that not only are the chances of a baby getting the disease following exposure to the bacteria far higher than in an adult, but the disease is more likely to be severe, often spreading outside the lungs.

Research supported by the NCRC is currently underway to understand why newborns react differently to adults when exposed to the bacteria MTB. Clinical Research Fellow Dr Cilian Ó Maoldomhnaigh (TCD), under the supervision of Prof. Joseph Keane (TCD) and Dr Patrick Gavin (CHI at Crumlin) is specifically examining the differences in immune response by examining the immune cells that fight TB infection. To do this, they are collecting blood samples from adults and from the umbilical cord immediately following birth and comparing the two.

Previous research indicates increased susceptibility in newborn babies is due in part to their poor or “immature” immune response to infectious agents. Cilian is particularly interested in macrophages, an immune cell that is important in fighting a TB infection. Macrophages work by digesting bacteria they encounter. This activity is dependent on macrophages being able to generate energy from their energy stores e.g. glucose. New research has shown the importance of metabolism, or the way that cells use energy, in generating an appropriate immune response in order to fight infection. This group are particularly interested in immune metabolism as it is an area not previously studied in babies.

In Cilian’s research project, he is assessing whether the immature immune response in newborns is due to how their macrophages generate energy. He isolates macrophages from the umbilical cord of newborn babies and adult blood samples, exposes the macrophages to MTB, and then compares how they use their energy stores as they attack the MTB bacteria. Early results are already showing differences, and Cilian’s next goal is to adjust the newborn’s macrophage responses by changing how they generate energy in order to help them destroy the TB bacteria more effectively.

The standard treatments for TB are over 50 years old and cases of multi-drug resistant TB are becoming increasingly common. There is therefore, a great need for new and effective treatment strategies for TB. Knowledge gained from Cilian’s research will make a valuable contribution to our understanding of the importance of the immune response in TB, and the specific role of macrophages in the process. This work has great potential to contribute to new treatments or vaccines for TB, to stimulate the best response, especially important for vulnerable children.
Immunity and Infection

The Impact of Overweight and Obesity on Inflammation and Immune Response in Children with Type-1 Diabetes

The rates of childhood obesity have trebled over the last few decades, now making childhood obesity a global epidemic. The World Health Organisation estimate that the number of overweight or obese children under the age of five has increased from 32 million in 1990 to over 42 million in 2015 and could reach 70 million by 2025. In Ireland, 1 in 4 children are either overweight or obese. This can increase their risk of developing life-threatening diseases later in life such as type 2 diabetes, cardiovascular disease, and cancer.

Like the general population, the rates of overweight and obesity are increasing in children with T1D. This represents a new problem as children with T1D who are overweight or obese are more difficult to manage clinically as they require more insulin than lean children with the same condition. Previous work from Eadaoin’s supervisors, Prof. Declan Cody and Dr Andrew Hogan, has shown that children who are obese are characterised by chronic inflammation and major changes in how their immune system works.

Eadaoin is investigating whether there are differences in the immune system of children with T1D who are obese or lean. More specifically, she wants to discover if there is a relationship between how the immune system functions and the doses of insulin required to manage T1D in these children. Knowledge gained from Eadaoin’s research will tell us how obesity is making it more difficult to manage children with T1D and potentially identify new targets for treatment which could resolve the complications of obesity in T1D.

Clinical Research Fellow Dr Eadaoin Hayes (UCD), under the supervision of Dr Andrew Hogan (NUI Maynooth) and Prof. Declan Cody (UCD and CHI at Crumlin) is investigating if changes in the immune system caused by obesity are making it more difficult to treat children with Type 1 diabetes (T1D). T1D is an autoimmune condition. This means that the immune system, which normally ignores healthy cells but destroys foreign substances that could cause illness, mistakenly launches an attack on the body itself. In the case of T1D, cells of the immune system destroy insulin producing islet cells in the pancreas. Insulin plays a key role in removing glucose from the bloodstream, thus removing blood sugars, while at the same time helping cells absorb glucose as a source of energy. Low levels of insulin in T1D lead to high levels of glucose in the bloodstream which can cause major complications, which is why the treatment of T1D requires the administration of insulin.

Award:
Clinical Research Fellowship

MD Student:
Dr Eadaoin Hayes

Team Leaders:
Dr Andrew Hogan and Prof. Declan Cody

1 in 4 children in Ireland are either overweight or obese.
Immediately following birth, babies are at increased risk of developing a bacterial infection. This risk is significantly higher in babies who are born prematurely. In severe cases, these infections can lead to neonatal sepsis, an exaggerated immune response to an infection within the bloodstream than can cause organ damage and even death. This incidence of neonatal sepsis is 1 case in 1000 for babies born at term but this increases significantly in preterm or very low birth weight babies to 26 cases in 1000.

In collaboration with clinical colleagues at CHI at Crumlin, the National Maternity Hospital (NMH) Holles Street, and the Coombe Women & Infants University Hospital, Dr Susan Knowles (NMH) and Dr Stephen Smith (Molecular Microbiologist at Trinity College Dublin) are leading a research project to collect and characterise bacterial samples associated with cases of neonatal sepsis within Irish maternity hospitals. The project will focus on cases of neonatal sepsis caused by the bacteria *Escherichia coli* (*E. coli*). It is the most frequent cause of neonatal sepsis. Its incidence is rising, and it is increasingly associated with severe infections, likely due to growing antibiotic resistance within this species.

Many variations of *E. coli* bacteria exist, with some associated with poorer clinical outcomes in cases of neonatal sepsis than others. Stephen’s research team aims to characterise *E. coli* strains that have caused neonatal sepsis using genetic, molecular, and functional tests. They will then look at the relationship between these results and the rates of poor clinical outcomes such as rupture of the amniotic sac prior to labour (preterm rupture of membranes), infection of the placenta or amniotic sac (chorioamnionitis), preterm birth, meningitis, damage to small and large intestine (necrotizing enterocolitis and/or perforated bowel), or foetal/neonatal mortality. This will allow them to identify the most dangerous *E. coli* strains.

To date, the team have established a bank of bacterial samples from cases of neonatal sepsis across the collaborating clinical sites. They continue to collect samples while extracting the genetic material from those already banked. Using this material, they are now in the process of characterising the different strains of *E. coli*. Once identified, they can examine how the different strains influence clinical outcome. This work will lead to a better understanding of the bacterial factors that cause more severe infections in neonates and may help clinicians identify newborn babies with the most dangerous strains of *E. coli* who are most likely to develop serious complications such as sepsis.
Immunity and Infection

Outcomes of modified exclusive enteral nutrition (EEN) in children with Crohn’s disease

Crohn’s Disease (CD) is a chronic inflammatory disease affecting the entire digestive tract. In Ireland, the incidence of CD in children has doubled since 2005 and continues to rise. It is a debilitating condition that has a significant impact on a child’s quality of life and can lead to major complications that can require surgical intervention. The exact cause of CD is unknown, but it has been linked with immune, microbiome (population of bacteria found in the body), and environmental factors. Increasing evidence also suggests that diet is an important contributing factor in CD.

Exclusive Enteral Nutrition (EEN) is a diet-based treatment for CD using a specially prescribed course of blended drinks for 6-8 weeks. It is associated with a higher rate of disease remission than steroid treatments. While effective, EEN is only a short-term solution for CD as its use is limited by issues with compliance, palatability, and the lack of additional treatments to sustain remission following the prescribed course of EEN.

Dr Seamus Hussey (UCD, RCSI and CHI at Crumlin) is a co-investigator on the M-EEN (Modified EEN) trial. This is an international trial comparing standard EEN to Crohn’s Disease Exclusion Diet (CDED) plus partial EEN. CDED is a whole food-based diet rich in fibre and resistant starches. It was developed by Prof. Arie Levine (Wolfson Institute, Tel Aviv, Israel), the lead investigator on the M-EEN trial. CDED has been shown to induce remission in up to 70% of patients and is associated with reduced systemic inflammation. In the M-EEN trial, Dr Hussey and his international collaborators will determine whether progression from EEN to CDED can lead to prolonged remission in children with mild to moderate CD.

In a sub-study, Seamus is also analysing the oral microbiome (the population of bacteria found in the mouth) in patients with CD participating in the M-EEN trial. Changes in the microbiome have been linked with the pathology of CD. Dietary therapy (EEN) has been shown to have a significant impact on the gut microbiome in patients with CD. Recent studies from Seamus’ research group show that 40% of children with CD have oral lesions. However, very little information is available on the relationship between the oral microbiome and clinical status in CD or the effect of dietary therapy on the oral microbiome. This sub-study of the M-EEN trial will determine if dietary treatments modulate the oral microbiome, whether profiles alter transiently or permanently following dietary therapy, or whether clinical remission influences the oral microbiome and can return it to a healthier profile.

In Ireland, the incidence of CD in children has doubled since 2005 and continues to rise.

Award: Paediatric Research Project Grant
Team Leader: Dr Seamus Hussey
Research Team: Dr Lenin Ekpotu (Research Assistant)
How small pieces of genetic material can influence cause and disease development in Eczema

Eczema, also known as atopic dermatitis, is the most common persistent inflammatory disease of early childhood. A total of 60% of cases of atopic dermatitis begin during the first year of life, and 85% begin before 5 years of age. It is caused by a combination of genetic and environmental factors, but the exact mechanisms behind the development of the disease are not fully understood.

A current research programme underway at the NCRC, led by Prof Alan Irvine and Dr Janna Nousbeck (TCD), is examining the genetic factors responsible for both cause and disease development in eczema. Specifically, their research program is examining microRNAs responsible for both cause and disease development in atopic dermatitis in children. MicroRNAs are small pieces of genetic material that play a crucial role in a vast number of biological processes because of their ability to regulate genes. However, little is known about microRNAs in atopic dermatitis. The major goal of this work is to identify unique disease-related microRNAs that are involved at early disease development and can influence the course of atopic dermatitis in children.

In this research, microRNA patterns are being investigated in blood taken from children with atopic dermatitis and compared to healthy children during their first year of life. This study was made possible because of access to a unique resource of blood samples from children with eczema attending CHI at Crumlin and from the umbilical cord of newborn infants from the BASELINE cohort study, previously supported by the NCRC. This study followed over 2000 babies from birth, collecting valuable clinical information and samples to allow a better understanding of why some children develop certain diseases.

The result of this work has been the identification of a unique pattern, or signature, of microRNAs associated with atopic dermatitis. Based on this information, Alan and Janna are now examining more closely the function of each microRNA to understand the cause and development of atopic dermatitis at a cellular level.

This unique signature of microRNA associated with atopic dermatitis will help to identify babies at risk at an earlier stage, allowing for intervention very early in life. Understanding the role of microRNA at a cellular level will inform the development of new, more effective treatments for children suffering from this very common disease.

A total of 60% of cases of atopic dermatitis begin during the first year of life.
24/7

The Biosample Storage Facility is monitored 24 hours a day, 7 days a week, and includes back-up storage facilities in case of emergency.
Laboratory Facilities

Overview

Laboratory facilities have been in place at the NCRC for over 50 years. Whether supported by NCRC research grants, or other, the facility is open to academic researchers, doctors, nurses and allied health professionals who are working in the field of paediatric research.

The facility is one of few places in Ireland that you will find researchers and clinicians from multiple Higher Education Institutes and paediatric hospitals working alongside each other. This provides a unique meeting point for academic and clinical researchers, promoting collaboration across disciplines as well as universities.

It is acknowledged internationally that best practice is to have a research laboratory on site to expedite the processing of precious patient samples, ensuring sample integrity. The NCRC serves this purpose, within minutes from the main hospital at CHI at Crumlin, the laboratory houses all of the state-of-the-art equipment required to allow the most advanced scientific techniques to be applied to the samples from children in the hospital. All research conducted uses patient samples that are obtained only after the research has been approved by an ethics committee, and consent has been obtained.

Dedicated laboratory staff operate the facility and ensures the highest standards of health and safety are observed, equipment is maintained, and that users are trained as appropriate.

The Laboratory also houses a biosample storage facility which is vital for the secure storage of precious patient samples. This facility houses several special freezers that can hold samples at extremely low temperatures, ensuring their long-term integrity. The system is monitored 24 hours a day, 7 days a week, and includes back-up storage facilities in case of emergency. This facility is managed by a dedicated laboratory team, who work with users to ensure the best standards are observed to maximise sample integrity and safety.
Clinical research in children is essential if we are to find new ways of preventing, diagnosing and treating childhood diseases. It ensures that children’s medicines and treatments are safe and effective, and that scientific advances can be made into the future. Most of the medicines currently given to children have only been tested in adults. However young adults, children and newborn babies often react differently to medicines than adults. Having access to clinical trials enables children to benefit from the latest advances in medicines and treatments.

Based at the NCRC in Crumlin, the CCRU staff work with Consultants at CHI at Crumlin and other paediatric centres to deliver cutting edge world leading research. Between April 2018 and March 2019, the CCRU supported 47 active trials and studies.

Between April 2018 and March 2019, the CCRU supported 47 active trials and studies.
CCRU Services

Conducting clinical trials in children is complex. The CCRU provides the paediatric specific supports required for Principal Investigators (PIs) to carry out the studies and to ensure this is done to the highest international standards. Services the CCRU offer include:

**Advisory Service**
CCRU offer PIs advice on conducting clinical studies in children, including protocol practicability, and information on local regulatory, ethical and operational requirements.

**Study Feasibility**
Through our Paediatric Investigator Network from hospitals across Ireland, we help identify potential study sites, connect Study Sponsors with Key Opinion Leaders and assist with pre-study visits.

**Study Set-up**
Experienced Study Coordinators are available to provide on-the-ground support to ensure streamlined study set-up, providing a central point of contact between the PIs, Study team, Sponsor and CCRU.

**Study Costing**
Study budget review and preparation of local study costings using Paediatric Study Costing tool to support commercial studies as well as Investigator led grant applications.

**Regulatory Affairs**
Appraisal of paediatric specific regulatory and ethics queries; assistance with HPRA and ethics submissions, assessment of study documentation including informed consent and assent forms and information sheets.

**Study Coordination**
Study Coordinators are the key operational contact between Study Sponsor (where appropriate), the PI and Clinical Study Team from study initiation interim conduct and study close-down. Project management services are also available for central coordination of studies across multiple sites.

**Quality Assurance**
The CCRU Quality Management System (QMS) based upon Good Clinical Practice (ICH GCP) Guidelines and all applicable regulatory and ethical requirements, ensures that research supported by the CCRU is conducted to the highest standards. Internal auditing and monitoring ensure compliance with the QMS.

**Trial Pharmacy**
With the support of the Hospital Pharmacy Department, a dedicated Trials Pharmacist is available to manage all aspects of research pharmacy including IMP and NIMP management and accountability.

**Paediatric GCP Training**
Paediatric specific GCP training courses are regularly conducted by our in-house GCP trainers along with an Introduction to Paediatric Clinical Research. Courses can be provided at other locations on request; all CCRU staff are fully GCP trained.
Cardiology

This research involves the study of a medical device, the Venus P-ValveTM. This cardiac device is used for the treatment of leakage (regurgitation) through the lung (pulmonary) valve, a condition that is very common in patients who have undergone previous heart surgery and have very limited treatment options available.

The most common therapy currently available involves open heart surgery to replace the defective pulmonary valve. As many of these patients are often young adults who have already undergone a variety of reconstructive surgeries since birth, the traumatic scars caused by valve replacement may further reduce cardiac function. In many cases it may be necessary to perform multiple operations (perhaps 3-5 over a lifetime) to replace valves with limited durability.

The Venus P-ValveTM is a prosthetic (artificial) heart valve device, made to replace a native defective lung heart valve.

The valve consists of a metal cage (stent) to hold the device in place and valve leaflets (made of tissue) help blood flow in the heart. Instead of undergoing open heart surgery, the Venus P-Valve is placed using a novel method of transcatheter implantation (tubes placed in the blood vessels).

This method of implantation could make the therapy less traumatic, which would reduce complications associated with operations as well as decrease the post-operative recovery time. The use of this method would also suggest that any repeat valve repairs or replacements could be achieved more safely.

The aim of this research study is to provide both short and long-term relief of the patients’ symptoms, improve cardiac function while delaying or removing future repeat open heart surgeries and improved quality of life.

The Cardiology Department in CHI at Crumlin is participating in this global Phase 3 study and currently has implanted the Venus P-Valve in nine children.

Principal Investigators:
Professor Kevin Walsh and Professor Damien Kenny

Study Coordinator:
Angela Scullion

Research Nurse:
Shiva Narang
Haemophilia

Haemophilia is an X-linked bleeding disorder resulting from a deficiency of factor VIII (Haemophilia A) or factor IX (Haemophilia B). Standard treatment presents many challenges and there is therefore, a significant need to improve treatments to enhance the quality of life and decrease the disease burden in patients.

The Haemostasis & Thrombosis (H&T) Department, CHI at Crumlin provides a service for all children in Ireland with bleeding disorders. Between 2012 and 2019 with the support of NCRC Services, the H&T Department at CHI, has successfully run a significant number of clinical studies. Across 13 separate therapeutic groups performing clinical studies at CHI with NCRC support, the H&T Department ranks second in total number of studies (n=17), including 15 Interventional clinical trials (industry sponsored) and 2 non-interventional (academic collaborative) studies. They have recruited 174 paediatric patients into the clinical studies (47 for Interventional clinical trials and 127 for non-interventional studies).

The majority of their trials have been based on replacement therapies with extended half-life products. Recently they have started new trials with the novel therapy called Fitusiran which rebalances the blood clotting system through increasing generation of thrombin, a factor which is crucial in blood clotting.

The aim of this research study is to target a specific group of patients who are difficult to treat with standard treatments. Patients on this trial have shown significant reductions in bleeding rates with no major safety events. They benefit from less frequent drug administration (once a month versus multiple times a week), decreased hospitalisations and significantly improved quality of life.

Principal Investigators:
Dr Beatrice Nolan

Senior Study Coordinator:
Kasia Fennel

Research Nurse:
Roisin Bradley, Antje Trainor & Aileen Molloy
The NCRC is committed to maintaining the highest standards of governance to ensure full transparency in how we operate. We are fully compliant with all relevant Irish Charity legislation and regulatory frameworks.

The NCRC is committed to the governance standards set out in The Governance Code for the Community, Voluntary and Charitable Sector in Ireland.

The NCRC Board has a key role in promoting and ensuring standards of good governance within the NCRC. The Board as a collective, and each member as an individual, has an important and challenging task to lead, direct and control the NCRC and to ensure that the governance objectives are appropriately fulfilled. Board and committee members are expected to observe the highest ethical and professional standards and to work constructively with the Chief Executive.
## NCRC Board Members
(active April 2018 – March 2019)

<table>
<thead>
<tr>
<th>Name</th>
<th>Position/Role</th>
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<tbody>
<tr>
<td><strong>Dr Ruth Barrington</strong></td>
<td>Chair of the NCRC Board</td>
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<tr>
<td><strong>Carol Hilliard</strong></td>
<td>Assistant Director of Nursing at CHI at Crumlin; Nursing Practice Development Coordinator, CHI at Crumlin</td>
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<tr>
<td><strong>William Shannon</strong></td>
<td>Accountant; NCRC Finance &amp; Audit Committee Chair</td>
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<tr>
<td><strong>Professor Jonathan Hourihane</strong></td>
<td>Professor of Paediatrics, UCC &amp; Consultant Paediatric Allergist, Cork University Hospital</td>
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<tr>
<td><strong>David O’Donohoe,</strong></td>
<td>Partner, Arthur Cox and NCRC Governance Committee Chair</td>
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<tr>
<td><strong>Professor Hannah McGee</strong></td>
<td>Dean of the Faculty of Medicine and Health Sciences at RCSI</td>
</tr>
<tr>
<td><strong>Professor Owen Smith CBE</strong></td>
<td>Professor of Paediatrics, UCD; Consultant Paediatric Haematologist, CHI at Crumlin; NCRC Strategy Committee Chair</td>
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<tr>
<td><strong>Professor Paul McNally</strong></td>
<td>Associate Professor of Paediatrics, RCSI; Consultant in Paediatric Respiratory Medicine, CHI at Crumlin</td>
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<td><strong>Joanne Ferris</strong></td>
<td>NCRC Nominations Committee Chair</td>
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<tr>
<td><strong>Professor Eleanor Molloy</strong></td>
<td>Professor and Chair of Paediatrics, TCD; Consultant Neonatologist &amp; Paediatrician, CWIUH, CHI at Crumlin, CHI at Tallaght</td>
</tr>
<tr>
<td><strong>Professor Con Feighery</strong></td>
<td>Consultant Clinical Immunologist, St James’s Hospital</td>
</tr>
<tr>
<td><strong>Professor Alf Nicholson</strong></td>
<td>RCSI Professor of Paediatrics and Departmental Head consultant Paediatrician based in CHI at Temple Street</td>
</tr>
<tr>
<td><strong>Professor Michael Gill</strong></td>
<td>Professor of Psychiatry and Head of School of Medicine at TCD</td>
</tr>
<tr>
<td><strong>Professor Frank Casey</strong></td>
<td>Consultant Paediatric Cardiologist in The Belfast Health and Social Care Trust, Northern Ireland Lead Clinician for All Island Paediatric Cardiology Network</td>
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The SAC is the second phase of scientific review of submitted grant applications. It provides an expert, constructive, and objective critique of the international peer-reviewed applications under consideration based on defined criteria such as alignment with NCRC priorities and strategy, productivity from other grants, quality of the right to reply document (Paediatric Research Project Grants) or candidate interviews (Clinical Research Fellowships). Following discussion, the SAC ranks the applications, and the highest-ranking proposals are recommended for funding. The recommendation of the SAC is then made to the Board of the NCRC for approval.
SAC Members
(Active April 2018 – March 2019)

**Professor Padraic Fallon,**
SAC Chair, Stokes Professor of Immunology, TCD

**Professor Fiona Alderdice,**
Senior Social Scientist at the National Perinatal Epidemiology Unit, Oxford, and Professor in Perinatal Health and Wellbeing at Queen’s University Belfast

**Professor Billy Bourke,**
Professor, UCD; Consultant Gastroenterologist, CHI at Crumlin

**Professor Maria Brenner,**
Associate Professor in Children’s Nursing, TCD

**Professor Frank Casey,**
Consultant Paediatric Cardiologist Royal Belfast Hospital for Sick Children Northern Ireland; Lead Clinician for All island Paediatric Cardiology Network; Visiting Professor Faculty of Life and Health Sciences, Ulster University; Honorary Senior Lecturer in Child Health, Queen’s University Belfast

**Professor Gloria Crispino,**
Founder and CEO of Statistica Medica Ltd.; Lecturer in Mathematics and Statistics

**Professor Paolo De Coppi,**
Consultant Paediatric Surgeon at Great Ormond Street Hospital; Clinical Reader and Head of Stem Cells and regenerative medicine at UCL Institute of Child Health, London

**Professor Con Feighery,**
Consultant Clinical Immunologist

**Dr Jacinta Kelly,**
Chief Executive of the National Children’s Research Centre

**Professor Mark Lawler,**
Chair in Translational Cancer Genomics and Dean of Education in the Faculty of Medicine, Health and Life Sciences at Queen’s University Belfast

**Dr Chris McCusker,**
Senior Lecturer and Director, Doctorate in Clinical Psychology, School of Applied Psychology, UCC; Consultant Clinical Psychologist/Neuropsychologist

**Professor Colm O’Donnell,**
Consultant Neonatologist National Maternity Hospital & CHI at Crumlin; Director, Clinical Research Unit, National Children’s Research Centre

**Professor Maureen O’Sullivan,**
Clinical Professor, TCD; Consultant Pathologist, CHI at Crumlin

**Professor Guillaume Sébire,**
Director of Child Neurology Division, Montreal Children’s Hospital; Full Professor, McGill University
The NCRC is financed predominantly by grants received from the Children’s Medical & Research Foundation (CMRF) Crumlin. In January 2019 CMRF Crumlin merged with the Temple Street Foundation to become the Children’s Health Foundation (CHF).

In the twelve-month period to the 31st March 2019, the NCRC received €4.6m in funding from the CMRF Crumlin and an additional €0.65m funding from various other external sources, totalling €5.25m.

2018/19 Expenditure

In summary of the total grant funding of €5.25m received in the period, circa 83% was allocated to direct research associated activity which included Paediatric Research Project Grants, the Children’s Clinical Research Unit, the Clinical Research Fellowship program, Innovation Awards, the Laboratory costs and other research activity. The remaining 17% relates to the costs associated with research grant award program management, communications, outreach, training & education and administrative support costs.

There were 61 active projects at the end of the period, with a further 11 projects approved still due to commence. Of the 61 active projects, there were 2 Leaderships Awards, 26 Paediatric Research Project Grants, 5 Innovation awards, 13 Clinical Research Fellowship awards and 15 Research Education Support/ IRC Awards postgraduate enterprise partnership awards.

2018/19 New Research Awards

During the period the NCRC issued New Research Awards totalling to circa €4.8m, details are as follows;

- 14 Paediatric Research Project Grant Awards totalling to €3.65m,
- 5 Clinical Research Fellowship Awards totalling to €0.95m,
- 3 Innovation Awards totalling to €0.15m,
- 6 Research Education Support/ IRC Awards totalling to €0.06m.

The New Research Awards focused mainly on Immunity and Infection (85%), Cancer (11%) and Cardiology (4%), with over 85% of the investment during the period connected with research at Children’s Health Ireland. Children’s Health Ireland is the new entity which now governs the three children’s hospitals in Dublin. In January 2019, the hospitals amalgamated and are called Children’s Health Ireland with hospital sites at Crumlin, at Temple Street, at Tallaght.

The Future

The NCRC Board and management is committed to invest in paediatric research in 2020 and beyond as a key strategic priority, subject to continued funding from the CHF and the donors and the fundraising community who support them.
Research Awards & Infrastructure Expenditure
for 12 months to 31st March 2019

- Research Grants: €2,521,034
- Children’s Clinical Research Unit: €666,406
- Laboratory Costs: €514,634
- Externally Funded: €642,447
- Indirect Research Costs: €904,977
- Training & Education: €14,754
- Communication & Outreach: €107,586
- Research Program Management: €171,267
- Administration & Corporate Management Costs: €611,370

Total Expenditure: €5.2M
# Index of Active NCRC Grants by Scheme

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<td>Alan Irvine</td>
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<td>Development of the Food Allergy Coping and Emotions (FACE) questionnaires for children, adolescents and young people</td>
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<td>Patrick Walsh</td>
<td>Séamus Hussey</td>
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<td>Defining the significance of altered IL-36 family expression in paediatric ulcerative colitis</td>
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<td>Billy Bourke, Séamus Hussey</td>
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<td>Roger Preston</td>
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<tr>
<td>Sarah Doyle</td>
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<tr>
<td>Brian McGuire</td>
<td>Kevin McCarthy, Patrick Kiely, Jennifer Stinson</td>
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<tr>
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<td>Ursula Fearon</td>
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<tr>
<td>Anthony Gerard Wilson</td>
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<td>Whole exome mapping of genetic variants linked with the development of chronic recurrent multifocal osteomyelitis</td>
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