TELETHON KIDS INSTITUTE
Discover. Prevent. Cure.

TELETHON KIDS CANCER CENTRE

Personalised, translational research for childhood cancers

CONTENTS

Telethon Kids Cancer Centre

Cancers in children are different from cancers in adults. They develop differently and can spread more rapidly and aggressively than adult cancers. Because cancers in children are not obviously linked to their lifestyles, it is difficult to pinpoint their causes.

The effects of these cancers can be devastating and long-lasting due to the toxic treatments children receive.

Defeating childhood cancer requires specialist teams of researchers and oncologists, and the Institute is proud that for over 25 years it has built such a team – the Telethon Kids Cancer Centre.

This Centre is part of an international network of cancer researchers that is delivering improved survival rates for children with cancer through the development of better treatments. This proven success provides genuine hope to children and their families, and continues to do so through excellence in research and clinical application.

Prof Jonathan Carapetis
Director | Telethon Kids Institute

Vision

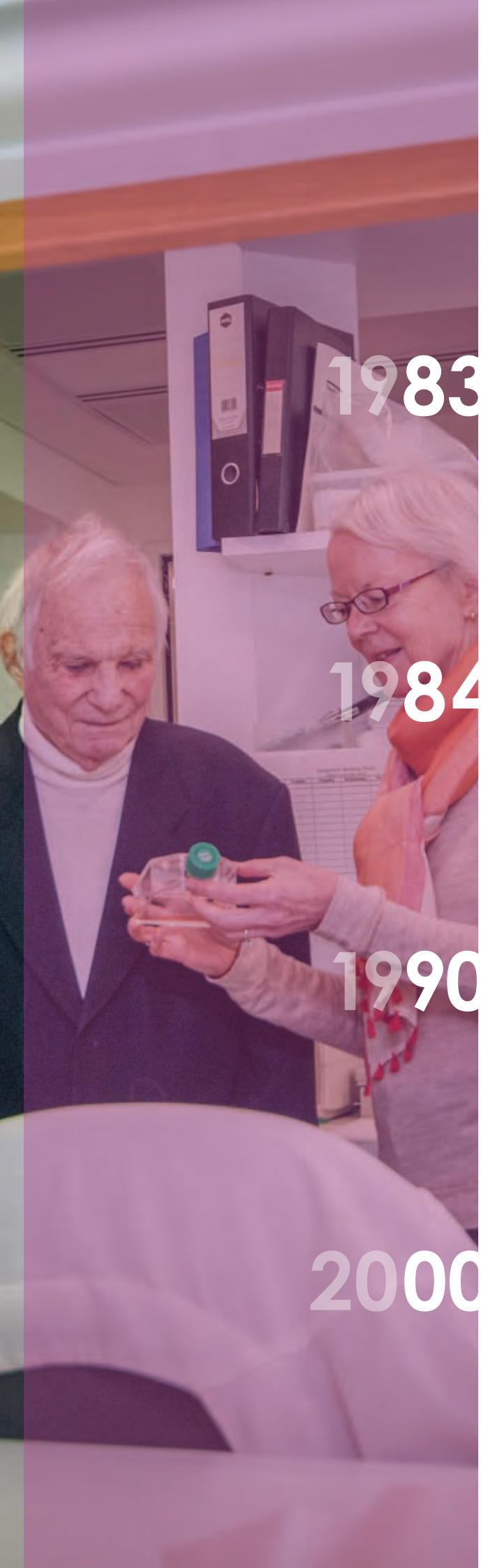
Despite remarkable medical advances over the past four decades, cancer is still the leading cause of death by disease in young people. Australian figures estimate that in 2016, 620 children will be newly diagnosed with cancer and 112 will die from this disease.

Cancer even takes a toll on those who are cured. Cancer during early life can have long-lasting impacts resulting not only from the disease itself, but also from its treatment. Survivors and their families face a large range of physical and psychological challenges, and some will suffer significant long-term effects for the rest of their lives impacting on their quality of life.

The Telethon Kids Cancer Centre is the sole Western Australian research centre dedicated to finding effective and safer treatments for childhood cancers. We strive for a future where no child will die from cancer, where survivors can live life to the full.

We also undertake major epidemiological studies that aim to identify factors that increase or decrease the risk of childhood cancers, with a vision of ultimately being able to prevent cancers happening in the first place.

In close partnership with the Perth Children's Hospital we are working to understand cancer and develop specific therapies to cure children with this disease. These therapies include better chemotherapies (both through the discovery of novel compounds and the repurposing of drugs already used for other diseases), radiotherapy, surgery and immunotherapy.



History

Prior to 1983, treatments for children with cancer in Western Australia were limited and largely palliative, not curative. Surgery with simple chemotherapy was attempted, yet many children died of their disease.

Professor Michael Willoughby arrived at Princess Margaret Hospital in 1983 bringing with him state-of-the-art cancer therapies. He founded the Total Care Unit which houses paediatric haematology and oncology, nursing, and allied care.

Professor Willoughby understood that in order to improve childhood cancer treatment, it is essential to study the biology of the disease at the same time. In 1984, he began a partnership with Professor Ursula Kees, who was researching cancer genetics. Consulting oncologists Dr David Baker and Professor Cathy Cole joined forces with Professor Willoughby and Professor Kees, and together they became WA's pioneers in translational medicine – transforming cancer treatment in the state.

When Professor Fiona Stanley established the Telethon Kids Institute in 1990, she cemented and fostered the growth of this critical relationship between scientific research and clinical practice. She was able to do this with the visionary and anchoring commitment of the Children's Leukaemia and Cancer Research Foundation, which has continued its significant support of the Centre annually.

Professor Stanley also recognised the importance of research into environmental and genetic risk factors and causes of childhood cancer, and in 2000 she recruited Dr Liz Milne to establish and lead the Cancer Epidemiology Program.

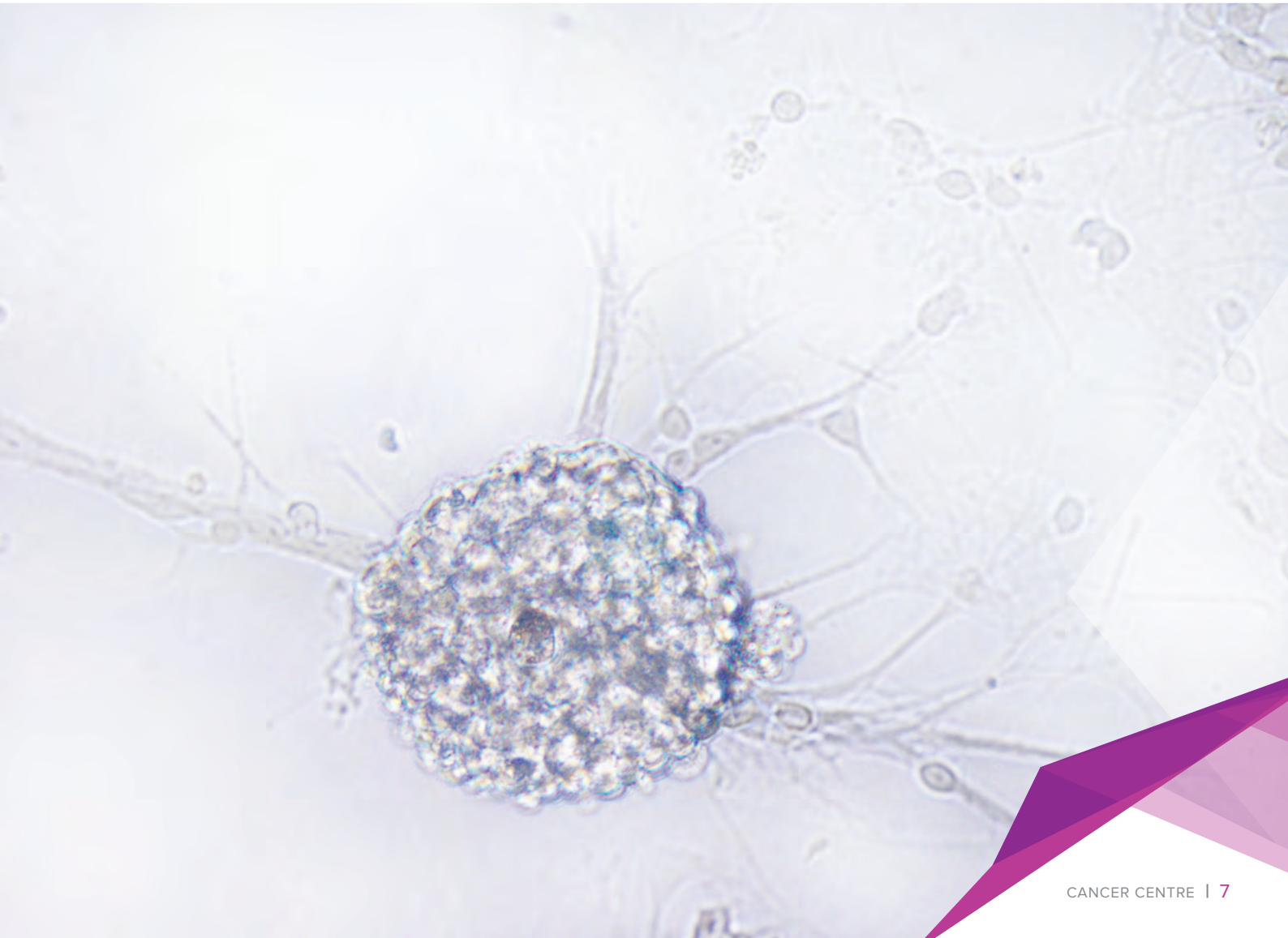
From those early days the WA childhood cancer research effort has evolved to include research programs in leukaemia, brain tumours, rare solid tumours, drug discovery, and prevention. These research programs are founded on a collaborative ethos between scientists and oncologists spanning such areas as genetics, molecular biology, systems biology, immunotherapy, radiotherapy, surgery and epidemiology.

What is Cancer?

Cancer is a highly complex multi-system disease, caused when cells within the body mutate and grow rapidly in an unregulated way. These cells evolve to compete with healthy cells, absorbing the very nutrients and oxygen that healthy cells require, and spread uncontrollably throughout the body.

If treatments are unsuccessful, this ultimately results either in organ failure or severe infection, leading to death. Unfortunately, cancer cells frequently evolve strategies to evade their own death with a resilience that healthy cells do not have, and hence can quickly become resistant to treatments that at first may look very promising.

We seek to discover vulnerabilities in paediatric cancers and develop therapies that destroy cancer cells while minimising harm to healthy cells. We also seek to understand more about environmental and genetic risk factors.



Childhood Cancer

Childhood cancer is the leading cause of death from disease in Australian children and adolescents. In most cases it appears to strike simply at random, and to date there is no way to prevent these diseases ahead of time.

In 2015, about 620 children aged 0-14 years were diagnosed with cancer in Australia. On average, 82 percent of these children will survive – but others will lose the battle.

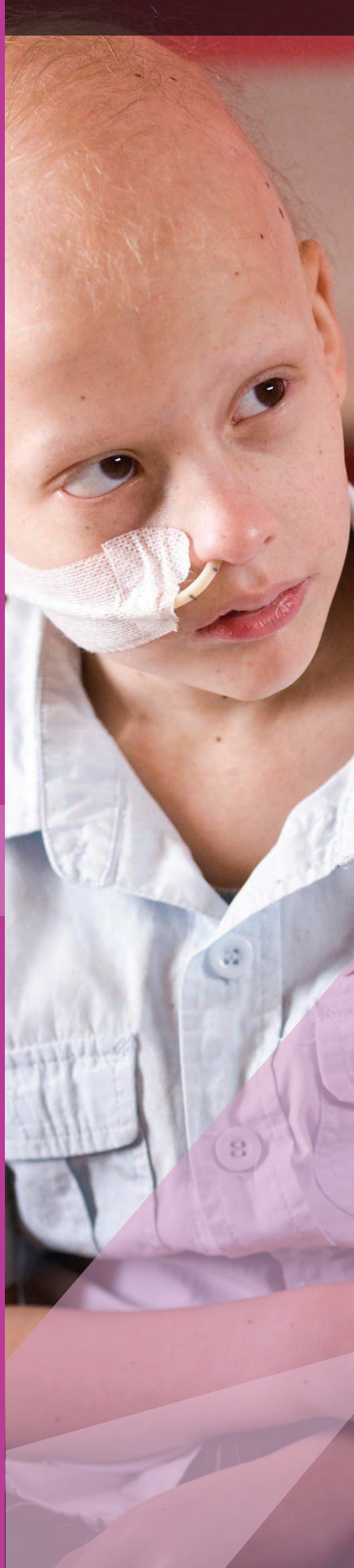
Childhood cancer patients are managed in the haematology and oncology departments of the major Australian paediatric hospitals, and participate in the world's large cooperative oncology trials. The results of these trials are shared widely to develop the best treatment strategies for children with cancer.

In Western Australia, 65 children are diagnosed with cancer annually, and about 53 of them will be cured with current treatments but are at risk of developing long-term side effects. The most frequently diagnosed childhood cancers are leukaemia and brain tumours, with these making up half of all diagnoses, both in Australian hospitals and world-wide.

In the last 30 years, survival for children with leukaemia has improved from 30 percent to more than 80 percent. This did not happen by accident, but is testament to the difference research can make.

Survival rates for brain tumour patients were similarly dismal several decades ago, but years of focused research are gradually leading to improved therapies. While survivors are often left with long-term problems resulting from toxic treatments – ranging from mental and behavioural health issues through to severe problems such as developmental delay, sterility, and an increased risk of other cancers developing subsequently – research is contributing to a better outlook for these patients as well.

These improvements have come about by involving patients in global research studies that directly link cancer biology research with clinical therapeutic strategies. Such studies are performed collaboratively between clinicians at Perth Children's Hospital and researchers at the Telethon Kids Cancer Centre as part of large national and international cooperative groups.



Personalised, Translational Research

Each cancer is unique, arising in distinct cells of the body and evolving with different combinations of mutations and strategies to evade cell-death. Even children with the same type of cancer will have different genetic features capable of triggering different responses to therapies. At the Cancer Centre we have always taken a precise and personalised approach to discovering new cancer treatments.

Researchers in the Centre specialise in several types of leukaemia, brain tumour and melanoma, as well as an extremely aggressive type of solid tumour known as NUT midline carcinoma. Embedded in each of these disease areas is our Centre-wide approach to discovering better treatments through improvements in chemotherapy, immunotherapy, and radiotherapy.

Precious cancer specimens (samples of blood or bone marrow, for example) are donated to the Telethon Kids Cancer Centre by patients at the Children's Hospital. Our researchers can then use these cancer cells to study the biology of the cancer, how it grows, how it responds to medicines, and why treatments sometimes do not work. This research brings us closer to our goal of finding the Achilles heel in each type of childhood cancer, so that with this information we can design better treatments for our young patients.

A Major Research Partner – International Children's Oncology Group

Professor Willoughby realised that in order to ensure WA patients had access to the very best cancer treatments, Princess Margaret Hospital would have to collaborate with other world-leading doctors. Under his leadership, in 1991 the Total Care Unit at the Children's Hospital became the first overseas-based member of the US-based Children's Oncology Group (COG). The COG has pushed the envelope in terms of childhood cancer treatment and has run more clinical trials for children with cancer than any other organisation in the world.

COG unites more than 200 children's hospitals, universities, and cancer centres across the globe to defeat childhood cancer. This means that every year, more than 14,000 children and adolescents diagnosed with cancer are enrolled in one or more clinical trials. These trials include front-line therapies, studies aimed at discovering the biological underpinnings of aggressive cancers, and trials involving new and emerging treatments and supportive care.

Membership in COG allows us to enrol our young patients in these international trials **and give them the same treatment offered in the world's premier cancer centres** – but without having to travel across the world to get it. Importantly, through these networks, discoveries made in our research laboratories can be rapidly shared to benefit children worldwide.

Research Areas

Genetics

The transformation of a normal cell into a cancerous cell involves changes to the processes that regulate normal cell growth and death. The critical pathways that are affected are distinct for each type of cancer. We are using the most modern genetic sequencing techniques to identify the critical changes that cause the uncontrolled proliferation of the cancerous cells. The ultimate goal is to design therapies directly targeting the Achilles heel of these cells.

Drug Repurposing

Many drugs currently available to adults with cancer – or to other patients with completely different diseases – have the potential to be effective in childhood cancer, yet have never been tested in this setting. This is partly due to the fact that cancers in adults and children are typically quite different, and treatment strategies have necessarily evolved separately. We are routinely screening thousands of such drugs to develop new therapeutic approaches for our cancer patients.

Drug Discovery

We are developing new drugs to target interactions between proteins, both inside and outside cells, which are thought to drive childhood cancers. We seek to achieve this by drawing from a massive collection of unique biological molecules called peptides, which are derived from primitive bacteria, some of which come from extreme environments like volcanic streams, geysers and deep sea volcanic vents which have evolved naturally into drug-like candidates. Interest in accessing this new class of peptides has resulted in discovery alliances with several large pharmaceutical companies from around the world, including Pfizer, Janssen, MedImmune/AstraZeneca and Roche/Genentech.

Epidemiology

We conduct studies to identify risk factors for childhood cancers with members of international consortia that allow analysis of large data sets to increase our ability to detect important risk factors. We also study the relationships between congenital anomalies and subsequent risk of cancers in childhood and adulthood, which will improve our understanding of causal pathways. The importance of folate metabolism and DNA damage are key focus areas. Some adult cancers, such as melanoma, are most likely caused by UV exposure during childhood and adolescence, and we are looking at effective ways of reducing harmful sun exposure during this critical period. We are investigating whether other cancers might be reduced through intervention in childhood. For example, vaccination or treatment for hepatitis B or C might be expected to reduce subsequent incidence of liver cancer.

Other areas of work include monitoring trends in the incidence of childhood cancer, the long-term consequences of cancer treatments, and identifying the psychosocial needs in cancer survivors.

Immunotherapy

Modern science is transforming how oncologists treat patients, by shifting from relatively non-specific toxic agents to selective, mechanism-based therapies. A successful example of this is immunotherapy, which endeavours to unleash the patient's own immunity to destroy tumours. The most promising immune-based therapies harness T cells, immune cells that recognise and marshal an attack against foreign invaders and diseased tissues. At the Cancer Centre we are generating a personalised vaccine to stimulate T cell immunity against an individual's unique cancer mutations. Furthermore, we are genetically altering tumour-attacking T cells to provide them with additional 'weapons' – rendering them more capable of eliminating cancer.

Systems Biology

Genes do not exist or function in isolation, they work together in networks. Systems biology employs mathematical modelling of genomic data to provide a holistic view of the biological networks that underpin cellular functionality and behaviour. These tools are being used by Cancer Centre researchers to decipher the mechanisms underlying cancer invasion and response to therapy.

Radiotherapy

It is essential to investigate radiation therapy alongside chemotherapy and/or immunotherapy to identify the best, most effective treatments for patients. To do so we use the X-RAD research platform. This laboratory-based targeted radiation tool is the only one of its kind in the Southern Hemisphere and will expedite the discovery of new cancer treatments with reduced side effects to normal tissues.

Computational Biology

The computational biology team focusses on understanding how every letter in our genome effects an individual's chance to develop diseases and modulates our individual responses to drug treatments. We develop computer algorithms as well as applying advanced machine learning techniques to large cohorts of in-house and public gene sequencing datasets. This work ultimately will lead to the routine application of "big data" approaches in the individualised treatment of human disease.

Research Strategy

Our central strategy for tackling these difficult diseases is to foster a culture of close collaboration between Western Australia oncologists and researchers. The unique relationship – between the doctors who treat children and the scientists who bring the latest knowledge and technologies to the clinic, all linked to networks of doctors and scientists around the world – provides a privileged framework within which to accelerate the application of new therapies. It also means that children with cancer in Western Australia are assured of getting the best care in Australia.

We are now in a new era of medicine, with the latest discoveries promising more effective treatments but with fewer side effects. **Before these new therapies can be given to children it is critical they be evaluated and proven to be safe and effective.**

Our collaborative approach ensures that this evaluation process makes new forms of chemotherapy, immunologic therapy, and molecular therapy available as rapidly and as safely as possible for children with cancer. Our expertise and knowledge in cancer genetics ensures that new treatments will only be administered to patients who stand to benefit, the very definition of modern personalised medicine.

We are also interested in the possibility of prevention. To that end, children at paediatric cancer hospitals around Australia have participated in our studies of environmental exposures, diet and genetic variants to improve our understanding of risk factors. These studies compare the experiences of children with cancer with healthy children to identify differences that may be related to cancer development.

DR RISHI KOTECHA

Collaboration is Critical

DR RISHI KOTECHA

Great medical advances happen when smart people ask tough questions. Dr Rishi Kotecha is one of those people. He is asking questions about which treatments are best for dealing with tumours that arise in the thin layers of tissue covering the brain and spinal cord.

Dr Kotecha has a dual perspective on treating cancer in children – he works both as a doctor on the hospital ward and a key researcher at the Telethon Kids Cancer Centre.

"The passion I developed for treating children with cancer developed during my training when I realised that a significant proportion of children with cancer could be cured," he says.

But collaborative research is key. And Dr Kotecha "walks the talk" by leading or being involved with many local, national and international research projects around childhood cancers. He supervises junior doctors and PhD students. He is across the most up-to-date research around the world and looks at ways to incorporate it into his work at Telethon Kids Cancer Centre.

"It is extremely beneficial to have a cancer research centre and a children's hospital co-located," he says, "as it enables collaboration between clinicians and laboratory researchers."

"It takes all of us working together to find the right answers."

Focus: Infant Leukaemia

PROFESSOR URSULA KEES AND PROFESSOR CATHY COLE

There's a photograph on Professor Cathy Cole's desk of a young woman wearing a white jacket.

"She had a really rough time with leukaemia, a bone-marrow transplant, lots of complications and we thought we were going to lose her several times in the last few years," says Professor Cole, consulting oncologist at the Perths Children's Hospital.

The sick child she remembers is now a healthy, 20-year-old university student. The photograph was sent to the professor by the girl's grateful mum. This young woman is just one of many survivors of childhood cancer.

The turnaround in survival rates, particularly with leukaemia, is one of the success stories in medical history. As recently as 1965 few children survived. These days, more than 80 percent of patients do. Worldwide, clinical trials that are testing different uses of well-known drugs, combined with better treatments to reduce side effects, have delivered stunning results.

But tragically, children under the age of twelve months don't enjoy the same odds, with only a 45 percent chance of survival. Chemotherapy, which ravages disease in bigger bodies, is often toxic in tiny ones. Side effects can include impaired intellectual capacity and stunted growth.

Finding a way to save these sick babies is a new frontier for childhood cancer specialists at Telethon Kids Cancer Centre, working in collaboration with other experts worldwide.

"It is glaringly obvious that this is a subgroup that needs specialist attention and we need to understand that better," says Professor Ursula Kees, Head of the Cancer Centre's Leukaemia Division.

Collaboration between the Cancer Centre's scientists and doctors treating patients at the Perth Children's Hospital is key.

"It's a two-way street the whole time," says Professor Cole. "So there is no delay in the translation of the biological findings into what's going on with the patients and the whole thing is just a continuous loop – and that's really ideal."

Patients' families are routinely asked if cancer specimens may be kept for research – none has ever refused. Consequently, the Telethon Kids Cancer Centre has an enviable bank of samples from patients – both sick and well – collected over the past 30 years.

Drugs not currently used in treatment of infant leukaemia have been tested in the Cancer Centre's laboratories on cell lines grown from these samples. Some have shown such promise that animal trials are underway.

"Testing is in progress, using eight of the conventional drugs, with three nominated new drugs," says Professor Kees. "We have really good hits to now follow up."

An international trial is the next step.

It is painstaking work only made possible by many important partnerships. Between doctors and their little patients. Between scientists and clinicians. And between researchers working in facilities all over the planet, sharing their knowledge.

"It is very exciting to see the pipeline coming through," says Professor Cole. "I'm hopeful we will be curing everybody within my lifetime."

The search continues so survivors like the young woman in the photo on Professor Cole's desk can go on to live full, meaningful lives.

And that white jacket the university student is wearing? It's a lab coat.

PROFESSOR CATHY COLE AND PROFESSOR URSULA KEES

Keep doing research! *It's good, and it works.*

Georgia Lowry

GEORGIA LOWRY

A Research Miracle

GEORGIA LOWRY

Georgia Lowry doesn't feel like a miracle.

"I feel like a normal, outgoing young lady," she says.

Call it a miracle. Luck. Fate. The simple fact is that, statistically, Georgia shouldn't be here.

Diagnosed at eight weeks of age with acute lymphoblastic leukaemia – a rare and aggressive form of cancer – Georgia's parents were warned it was likely their little girl wouldn't make it. Indeed, doctors gave her a very slim chance of survival.

"I thought I just had a sleepy, perhaps virally baby. Instead, I had a critically unwell baby," says Ann-Marie Lowry, Georgia's mum.

"Georgia was very unwell and in the newborn intensive care unit," remembers Professor Cathy Cole, consulting oncologist at the Perth Children's Hospital. "Her very young age made giving chemotherapy difficult and increased the risk of infection."

"I met the family, especially Ann-Marie and Georgia, shortly after she was diagnosed," says Professor Ursula Kees, who directs the Cancer Centre's leukaemia research. "I remember a very sick child and a distraught mother, of course."

"At the time, my resolve was that Georgia was one of a very special group of infant patients who needed particular attention, and we were going to renew our research efforts to find out how to best go about treating this disease and learning why it was so aggressive."

A bone marrow transplant was considered Georgia's best chance of survival. So, at six months of age, she became the youngest patient to undergo the procedure for leukaemia in Australia. Her 2-year-old sister, Grace, was the donor.

Georgia's recovery was slow and complicated. Many months and many trips to the Intensive Care Unit later, things looked hopeful.

Then, a checkup revealed a new and terrible reality.

"The blood technician wouldn't let me see the results and he kept making excuses for it," remembers Ann-Marie Lowry. "He wouldn't look me in the face, wouldn't talk to me. Then the doctors came to see me and I knew."

The leukaemia was back.

If the initial diagnosis was devastating, the relapse seemed to eliminate all hope.

"I'd been to too many funerals..." recalls Ann-Marie Lowry, "I said, 'You're kidding?' and he said, 'I'm sorry.'"

The family took a holiday together that they hoped wouldn't be their last. Doctors weren't optimistic but gave Georgia big doses of steroid treatments to take while away.

Ten days later, blood tests revealed she was back in remission. The decision was taken to attempt a second bone marrow transplant.

Again, Grace was her sister's donor. And this time, it worked. From the age of around three and a half, Georgia was able to get back to existing as a normal kid. Climbing trees, riding ponies, getting dirty, having fun with her big sister and baby brother.

Still, the treatments have taken their toll. Chemotherapy and radiotherapy stunted Georgia's growth, affected her hair, teeth and some organs. But her character is undiminished. She has often been called "a miracle", although it's not a label that sits comfortably with the 22-year-old.

"When I think about it, I guess I am, but I'm just living my life," Georgia says. "I just think about all the other people who didn't get to or are struggling."

Professor Kees says Georgia's leukaemia cell lines are still being used in the labs at Telethon Kids Cancer Centre and around the world through collaborative networks to try to find a cure for leukaemias like the one that threatened Georgia's life.

"Georgia and her family have been generously providing samples," says Professor Kees, "and they have been used to probe deeper into her disease, to get closer to what actually led to the disease that threatened Georgia's life."

"Her leukaemia cells can be grown in the laboratory and used to help to try to find a cure."

That critically ill baby has now grown into a diminutive but strong young woman who competitively jumps horses for fun and unashamedly seeks out joy.

Georgia has a job as a disability support worker and also volunteers with a charity helping teens with cancer. And, Georgia was named a state finalist for the Young Australian of the Year.

ANN-MARIE LOWRY, PROFESSOR CATHY COLE, GEORGIA LOWRY AND PROFESSOR URSULA KEES

"My outlook on life is to live life to the full. I don't feel that I'm any more special than anyone else," says Georgia.

But she considers that researchers are special. At a Telethon Kids Institute event in 2015 Georgia was asked to speak and said, "Keep doing research! It's good, and it works."

In many ways, Georgia's story tells the story of the Telethon Kids Cancer Centre. She has been associated with the Centre almost from its beginning. Her case typifies the quality of translational research that flows naturally between bench and bedside, between laboratories and the clinics. It demonstrates the collaborative research the Centre undertakes globally. And it exemplifies the passion and motivation of the Centre's cancer researchers, demonstrating how connected researchers are to the children they are working to help cure.

"It is a miracle Georgia is with us," says Professor Ursula Kees. "She is very special to us. She keeps our confidence alive that there is a cure for patients just like the 2-month-old Georgia of 22 years ago. We never give up working towards that goal."

Achievements

- Through its high quality research and links to clinical practice, the Telethon Kids Cancer Centre has helped improve the childhood cancer survival rates in WA from 30 percent in 1983 to more than 80 percent in 2015
- Co-discovered the homeobox gene HOX11/TLX1 that drives T cell leukaemia in children. Developed better diagnostic methods for patients with leukaemia by studying the genetic signatures of patients enrolled on COG therapy protocol
- Studied the important role of the p16 gene in leukaemia and examined many drugs for their efficacy in childhood leukaemia, making use of our large panel of cell lines that can be grown in the laboratory
- Demonstrated that leukaemia cells can accelerate disease by inducing normal cells to assist in promoting their growth
- Identified novel drug combinations in pre-clinical models that are effective in treating infants with leukaemia, where survival rates remain poor
- Established one of the oldest collections of cancer samples in Australia that all researchers can access to make new discoveries
- Described, for the first time, a rare and incurable form of cancer called NUT Midline Carcinoma, which affects both children and adults, leading to the development of a diagnostic test for the disease
- Performed a world-first study of the genetics of NUT Midline Carcinoma, reported the mutations driving this aggressive disease, and identified more effective drugs for therapy
- Established the largest laboratory in Australia with a specific focus on malignant brain cancers in children
- Introduced new research methodology to Australia that allows the study of living childhood brain cancer cells in the lab
- Initiated a global network of clinicians and researchers with a focus on curing the brain cancer medulloblastoma

- Developed a drug discovery pipeline to find and test new treatments for fast growing and lethal brain cancers
- Developed a novel pre-clinical model of cutaneous metastatic melanoma that more closely mimics human disease
- Identified the key immune cells responsible for generating an effective anti-T cell immune response against melanoma
- Developed a platform to engineer better tumour-attacking T cells
- Developed the most potent known inhibitor against MYC – the most widely overexpressed oncoprotein
- Developed a new class of peptide known as "Phylomers" for more efficient delivery of biologics drugs ("smart drugs" like proteins and nucleic acids) into cancer cells
- Reported for the first time that accelerated fetal growth was associated with an increased risk of acute lymphoblastic leukaemia, irrespective of absolute birth weight, and confirmed these findings in an international pooled analysis of data from 12 countries
- Identified for the first time an increased risk of childhood brain tumours associated with professional pesticide use in the home in the months leading up to conception
- Identified for the first time that maternal use of folic acid supplements before and during pregnancy was associated with a reduced risk of brain tumours in the child
- Identified that fathers' intake of alcohol around the time of conception may increase the risk of brain tumours in the child, suggesting that fathers as well as mothers should reduce alcohol intake when planning a pregnancy
- Identified the epidemiological and prognostic features for child and adolescent meningioma and defined the first evidence based therapeutic guidelines including the recommendation for aggressive surgical management, to achieve gross total resection, as the initial treatment of choice

The Memphis Connection

DR RAELENE ENDERSBY AND DR NICK GOTTARDO

Memphis, Tennessee is known as the birth place of rock and roll and home to Elvis Presley. But there's an institution there as famous within the medical world as Graceland is to music fans.

St Jude Children's Research Hospital in Memphis enjoys a reputation as one of the world's foremost facilities for researching and treating childhood cancers.

And at the Telethon Kids Cancer Centre, adopting the St Jude model where research is embedded in clinical care and vice versa has yielded impressive results.

Exciting, pioneering work on new ways to treat children with aggressive brain tumours is now being conducted by the Telethon Kids Cancer Centre team, headed by two experts who also happen to be St Jude's alumni.

"I went to Memphis to gain specialist training in childhood brain tumours," says Paediatric Oncologist, Dr Nick Gottardo, "both to learn about cutting edge laboratory research and also to be exposed to a world class centre of expertise in paediatric brain tumours."

He was impressed with the facilities and the research underway there. "The hospital was like an oasis, it was an incredible place," says Dr Gottardo.

More than 100 children aged 0-14 die from cancer in Australia each year. One in four of these deaths is a child with brain cancer. Brain tumours are the most common form of solid tumour occurring in children.

Perth research scientist Dr Raelene Endersby trained under Western Australia's Chief Scientist, Professor Peter Klinken, before seeking to further her work somewhere extraordinary. Dr Endersby also went to St Jude and was part of the brain tumour program, specialising in developmental neurobiology.

Dr Endersby learned new techniques working in the lab of her mentor, Dr Suzanne Baker, an eminent scientist specialising in difficult-to-treat brain tumours.

"She works on high grade gliomas in children and especially those that are particularly aggressive," says Dr Endersby. "Diffuse intrinsic pontine glioma is a lethal cancer in children, there are no treatments that are effective."

> *There are very few labs that **test new drugs for children's brain tumours** like we do.*
>
> Dr Endersby

DR RAELENE ENDERSBY AND DR NICK GOTTARDO

“It’s a very invasive, fast-growing tumour that grows in the brain stem and because it’s in that part of the brain, it can’t be removed by surgery.”

Remarkably, while Dr Endersby and Dr Gottardo didn’t cross paths in Western Australia, they did in Memphis.

“We got to know each other, respected one another’s work,” says Dr Endersby. “Nick was working on two diseases – medulloblastoma and ependymoma – and I was working on these high grade gliomas.”

After Dr Gottardo returned to Perth, he recruited Dr Endersby as co-leader of the Brain Tumour Research Program at the Cancer Centre. Together, they were able to develop a world-leading research program with the dedicated financial backing of the Telethon Adventurers.

Using the St Jude model, where clinical practice and research work “hand in glove”, the team has identified a new class of drugs, developed for use in adult cancer but not previously used in children, that shows great promise.

“We’ve established a pipeline of research using donated tumour tissue that we get from patients at the Children’s Hospital,” says Dr Endersby. “We used those cancer cells and screened almost 4,000 drugs.”

“We found a group of these drugs that not only work very well but they improve the current treatments we have in the clinic.” Already, pre-clinical trials have been positive.

“What we do is we take the tumours from the patients at the time of surgery and we implant them directly into the brain of pre-clinical models,” explains Dr Gottardo. “It corresponds to the same location where the tumour came from in the child. In essence we’re creating an Avatar of the patient’s tumours. Using these models, we can test new therapies and identify new medicines that have promise for our patients. Our ultimate goal is to assess our most promising drug candidates in clinical trials for children with brain tumours.”

The team is currently in discussion with pharmaceutical companies about running an international trial. “With the innovative tools that we’ve developed, there are very few labs that test new drugs for children’s brain tumours like we do,” says Dr Endersby.

These tools include the pre-clinical models and tumour samples on which drugs can be tested. As well, an enviable collection of sophisticated equipment – imaging machines that allow scientists to track tumours, microscopes used on living cells, and high throughput robotics – allows them to do experiments with combinations of drugs in a rapid manner.

They routinely consult and collaborate with colleagues around the world – including those at St Jude – to push the boundaries of what’s possible in child brain tumour research.

“We’re a lab that’s been born out of global collaborations and the generosity of our colleagues around the world wanting to help us out to make the best lab that we could be,” Dr Gottardo says.

To Roman Catholics, St Jude was the Patron Saint of hopeless causes. What drives the Centre’s brain tumour team is an urgent desire to prove that saving children from this cruel killer is a case that’s anything but hopeless.

Discovering Drugs with Nature's Tools

PROFESSOR PAUL WATT

Professor Paul Watt and his team at the Cancer Centre's Drug Discovery Unit (DDU) work at the cutting edge of scientific discovery, targeting cancer causing proteins which have proven out of reach of conventional therapies. In order to thwart a protein that feeds more than 70 percent of cancers, they sought inspiration from nature.

Over billions of years, viruses and bacteria have developed penetrating protein 'keys' in order to enter and invade the human cells they infect. The DDU team hijacked this cell entry mechanism to deliver protein-based therapies into cells. In order to hunt for such keys governing cell entry, they 'harvested' the genomic information of more than 35 bacteria and viruses to create a 'library' of more than 100 billion distinct gene fragments.

These mini genes encode a repertoire of billions of distinct peptide shapes called 'Phylomers'. Rare members of this Phylomer library have precisely the right shapes to bind to particular cancer proteins blocking their assembly into the machinery driving the growth of tumours, acting as highly selective "smart drugs". Other members can act as keys to enter cancer cells.

The capacity to find the Phylomer smart drugs and combining them with Phylomer 'keys' delivering them into cancer cells has enormous potential for the development of safer more effective cancer drugs by allowing for smaller therapeutic doses with reduced potential for toxic side effects.

"Normally the defenses of the cell have evolved to keep foreign stuff out of the cell," explains Professor Watt, "and even if foreign bodies do manage to get inside cells, then they remain trapped in a compartment known as an 'endosome' where they can't do us any harm." This natural defense mechanism presents major challenge for smart drug delivery as the therapeutics can also become entrapped within endosomes once they get into cells.

"We can wheel in the Trojan horse, but we want to get the warriors out to fight Troy, so we've screened for a way of finding very rare peptides in the library – literally one in a billion –which are capable of getting into the cell and out of the endosomes. Not only is our Trojan horse capable of entering the cancer cell (Troy), but it is also able to release the agents to kill that cell once inside."

It's an innovative approach to killing cancer cells that already has attracted the attention of some of the planet's biggest pharmaceutical companies.

But Professor Watt's enthusiasm is more altruistic. "One of my goals is to retire knowing that I've done something that has a real impact on child health," he says.

"I think it is a privilege to work with a powerful team of smart scientists within the Telethon Kids Cancer Centre, and to see the fruits of our labours, to witness some concepts that we might have drawn up on a white board a couple of years ago, become a reality."

"It's satisfying when the scientists in the lab know that they were part of something that's internationally relevant."

It's satisfying when the scientists in the lab know that they were ***part of something that's internationally relevant.***

Professor Watt

PROFESSOR PAUL WATT


“I am keen to **make a difference** by identifying risk factors that will contribute to preventive efforts.”
Professor Milne

PROFESSOR ELIZABETH MILNE

The Role of Childhood Cancer Epidemiology

PROFESSOR ELIZABETH MILNE

f we don't know what increases the risk of a particular cancer, how can we prevent it?

Epidemiology aims to answer these questions.

The term derives from several Greek words – epi meaning "on" or "upon", demos meaning "people" and logos meaning "the study of" – literally, the study of what is upon the people.

In cancer epidemiology, experts like Professor Elizabeth Milne, who heads the Cancer Centre's Epidemiology Group, are attempting to identify factors that may increase the risk of cancer in children.

"Some of these risk factors may be amenable to change – for example, there is some evidence fathers smoking in the lead up to pregnancy, home pesticide use, pregnant mums' diet and use of folic acid supplements might impact on the cancer risk to children," says Professor Milne. "The aim is to identify these things and – when there is enough evidence – to communicate these findings to the public and recommend changes in behaviour."

Professor Milne is currently leading an international, pooled analysis looking at maternal consumption of various drinks during pregnancy and the subsequent risk of leukaemia in the offspring. By sharing evidence, it means that stronger, statistically-supported conclusions can be drawn and that risk factors can be easily explained.

Each generation knows more than the last. And today's babies and young children have a better chance of living healthy lives than those before them. Epidemiology has made a major contribution to this.

Fifteen years ago, Professor Milne was recruited by fellow epidemiologist Professor Fiona Stanley to establish and lead a cancer epidemiology program at Telethon Kids. After a very productive 15 years, her passion for unearthing answers is still strong.

"I am keen to make a difference by identifying risk factors that will contribute to preventive efforts," she says.

The Potency of Immunotherapy

DR JASON WAITHMAN

If we liken fighting cancer to a war, the Telethon Kids Cancer Centre is ordering the science of immunotherapy into strategic combat on two fronts.

The first is developing a cancer vaccine for a preventative strike. Unlike conventional immunisation developed for populations, this would be a vaccine personalised to an individual child's cancer. The vaccine would help that child's body recognise the cancer cells as foreign and then command an army to fight them.

"We have recently found that two 'commanding generals' in our immune system are responsible for instructing and directing an army of soldiers (T cells) to fight a common enemy (cancer cells)," says Dr Jason Waithman. "This is an important find."

"We are now conducting experiments to gain more insight into where these two generals are located within the body and how they direct their armies. We are using this information to provide instructions to these generals (these instructions are the vaccine) in order to win the war."

The second battlefield front uses a treatment called adoptive cells therapy, where researchers are engineering better cells for therapy. T cells – or soldiers – are taken out of the body and grown in the laboratory, allowing researchers to assemble billions of cancer-killing cells.

"Tumour-attacking warrior cells that kind of engage them in hand-to-hand combat, if you like," explains Dr Waithman.

"Before putting these back into the patient, we are engineering them to secrete molecules capable of improving their own activity, recruiting other members of the immune system, and overcoming the repressive tumour environment."

Already, clinical trials have yielded amazing results.

"About 70 percent of people have had a complete response," says Jason Waithman. "There are stories of people's tumours melting away in weeks and days. This is very, very exciting therapy."

And already it's being tested in various cancers – leukemia, melanoma and paediatric brain tumours.

"Winning the war? We're working on it," says Dr Waithman.

Winning the war? **We're working on it.**
Dr Waithman

DR JASON WAITHMAN

Targeting the Highly Aggressive NUT Midline Carcinoma

ASSOCIATE PROFESSOR ALEX BEESLEY AND DR ANJA STIRNWEISS

Imagine, for a moment, that a human cell can be likened to a ping-pong ball. In ordinary circumstances, its size, weight and perfect spherical shape allow it to be used for its intended task – namely, playing ping-pong.

Now, imagine that for some reason, someone has tampered with the ball. Squashed or stuck a piece of chewing gum to its smooth side. Even something as innocuous as a tiny dimple can have an impact. Whatever the change, the ping-pong ball no longer flies easily through the air. It won't do what it's supposed to.

So it is with human cells. Sometimes they form incorrectly or develop unusual characteristics. And these aberrations, at a genetic level, occasionally lead to cancer.

What causes the alterations? How do we stop them in the first place? Is there a treatment that will change the ping-pong ball back to its original shape?

These are some of the questions attempting to be answered by Associate Professor Alex Beesley and Senior Research Associate, Dr Anja Stirnweiss, at the Telethon Kids Cancer Centre.

Their small team is investigating a rare, fast-growing and aggressive cancer known as NUT Midline Carcinoma (NMC). This cancer received its curious name because it develops around a particular gene called the NUT gene. In early cases, the tumour presented in the organs and tissues in the mid-line of the body from the diaphragm upwards; hence, it became known as NUT Midline Carcinoma.

A/Professor Beesley and Dr Anja Stirnweiss are focusing on using new techniques in attempting to ascertain what has gone wrong on a molecular level, in the hope of finding a cure.

In particular, they are conducting genetic sequencing on the tumour to identify the specific changes that have caused the cells to turn cancerous. "This is where precision medicine, personalised medicine is headed," says A/Professor Beesley.

The first patient in the world ever recorded with the tumour that came to be known as NUT Midline Carcinoma, presented at Princess Margaret Hospital in 1991. Since then, about 120 cases have been recorded worldwide. No one has survived the disease. After diagnosis, typical life expectancy ranges from three to nine months. There is no treatment and no cure.

Yet.

The Telethon Kids Cancer Centre is at the forefront of sequencing the NUT Midline Carcinomas, as well as testing drugs on cell lines taken from these tumours, to see if any known drugs can either kill the cancer or buy time to treat it.

A/PROFESSOR ALEX BEESLEY AND DR ANJA STIRNWEISS

> *There won't be an overnight cure, but what you do is* **you push the envelope with each experiment.**
>
> A/Professor Beesley

"We have now a unique panel of about 12 NMC cell lines, which is a large number for such a rare condition," says A/Professor Beesley, "and so we have been doing drug screening on those cell lines to see which drugs are most effective.

"We always feel as though we're in a race before the next child presents with NMC."

Knowledge generated by the team is shared with other world experts, and there is now a central registry for patients in Boston, Massachusetts. Already a new class of drug is showing promise. Known as Bromodomain – or BET inhibitors – it targets the major genetic mutation associated with NMC tumours.

"These BET inhibitors are really hot in cancer at the minute," says A/Professor Beesley, "and they're using them in all types of cancers. However, they were originally designed to target the defect found in NMC. They are now in clinical trial."

While some researchers might be tempted to put difficult conditions like NMC in the "too hard" basket, its complexity only serves to fuel the Telethon Kids cancer researchers' passion.

"Usually such rare diseases have a really poor outcome and there's not enough research being conducted in these areas," says Dr Stirnweiss. "So I think this research is a really good opportunity to make a big impact on someone's health and well-being, and potentially save their life."

"Forty years ago leukaemia was fatal, just like this disease is fatal," says A/Professor Beesley, "so I am very optimistic. There won't be an overnight cure, but what you do is you push envelope with each experiment."

Research Team

Within Telethon Kids Cancer Centre, there are approximately 65 laboratory scientists, epidemiologists, clinical researchers, computational biologists, bioinformaticians, PhD students and research assistants working in partnership with the following core leadership team:

A/Professor Alex Beesley, PhD

Dr Anthony Bosco, PhD

Professor Cathy Cole, MB BS W.Aust., FRACP(Paeds), FRCPA(Haem)

Dr Mark Cruikshank, PhD

Dr Raelene Endersby, PhD

A/Professor Nick Gottardo, MBChB FRACP PhD

Professor Ursula Kees, PhD

Dr Rishi S Kotecha MBChB MRCPCH FRACP PhD

Dr Timo Lassmann, PhD

Dr Nadia Milech, PhD

Professor Elizabeth Milne, PhD MPH

Dr Jason Waithman, PhD

Professor Paul Watt, DPhil

Strategic Partners

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Giving

The Telethon Kids Cancer Centre is supported by many wonderful people and organisations who give independently, through their own fundraising activities, or through various supporting charities, including the Ethan Davies Fellowship, Telethon Adventurers, Bright Blue, Rotary, Tour de Cure, and the Children's Leukaemia and Cancer Research Foundation (CLCRF).

For information on supporting the Telethon Kids Cancer Centre, please call +61 8 9489 7945 or email development@telethonkids.org.au

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