

# Childhood blood cancer

The quest for  
a kinder cure



## About the author, John Illman

Previously: founder editor, New Psychiatry; editor, GP; medical correspondent, Daily Mail; health editor, The Guardian; medical correspondent, The Observer; visiting lecturer in science communication at the University of Cambridge.

John's seven books include *The Body Machine* with heart transplant Professor Christiaan Barnard; the award winning *Use your Brain to Beat Depression* and

the most recent, *Handling the Media: Communication and Presentation Skills for Healthcare Professionals*.

He is now working as a freelance writer, media and presentation skills trainer, facilitator and visiting lecturer in medical journalism at the University of Westminster. He also has extensive broadcasting experience.

John writes: "Knowing people with blood cancer I want to do all I can to highlight the need for more effective and gentler treatments, especially for children. From the outset I felt extremely committed to this report and I hope the report reflects that."

"Freelance writing is a lonely business. It is a wonderful experience for someone like me to feel as if they have been adopted into a caring community like Bloodwise. Thank you Bloodwise. I would also like to thank the parents, patients and researchers who have given me that most precious commodity of all – their time."

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# A Foreword by Nick Clegg and Miriam Gonzalez Durantez

Antonio, our eldest son, was 14 when we first spotted a small, entirely painless lump in his neck. Although he had no other symptoms, we made an appointment with our local GP.

We were lucky: our brilliant doctor quickly recognised that the lump could be something more serious. And so it was that after an ultrasound scan and a biopsy Antonio was diagnosed in September of last year with stage 2 Hodgkin lymphoma in his neck and his chest.

Like all parents who have a child diagnosed with cancer, our first reaction was an overwhelming, if irrational, wish to take the cancer away from him and take it on ourselves. But of course you can't. You have no choice but to watch your own child battle through the heavy treatment, however much all your parental instincts wish you could take their place.

The treatment he received in the NHS at the teenage cancer unit at UCLH was superb. Every single person working on the ward – from the reception desk to the expert nurses – was friendly, professional and compassionate. We were especially fortunate that Dr Stephen Daw, Antonio's Consultant Oncologist, is a specialist in childhood and teenage lymphomas and

leads research into improving treatments and outcomes.

Antonio had four monthly cycles of chemotherapy, undertook a course of very heavy steroids and was prescribed a barrage of medication including antibiotics and pills to tackle nausea. At one point his treatment meant he was taking over 20 tablets per day.

The side effects that he experienced were what you would expect, including complete hair loss, vomiting and extreme tiredness. At one point he was neutropenic, meaning that his body had no defences against possible infection.

But by the end, the treatment appears to have had exactly the effect we hoped for: Antonio is free of cancer, and his regular three-monthly checks have detected no return of the disease.

Not everyone is so fortunate. Hodgkin lymphoma affects around 2,000 people every year in the UK. The risks of the disease are highest amongst the elderly and young adults. It is rarer amongst children. For those



who do make a full recovery, the treatments can nonetheless be very harsh and can have detrimental long-term side effects.

So clearly there is scope to treat childhood blood cancers even more effectively. With the financial support of Bloodwise, Dr Daw is leading research to improve the recovery rates for lymphoma – which are already high compared to other cancers – and reduce the unpleasant and long term side effects. This report outlines an exciting range of research being undertaken to develop new treatment and kinder cures. Treatments which could lead to a reduction in radiotherapy and even chemotherapy and which no longer come with the risks of short or long term life-changing, even fatal, side-effects. More research is needed to understand these conditions better and develop the way we treat them.

We know how lucky our family has been. The experience of being a cancer patient changes a person forever, even if they make a full recovery. We are immensely grateful to everyone who helped Antonio. That is why we are proud to support the work of Bloodwise, and the research conducted by Dr Daw and others in his field, in helping to discover better cures for childhood blood cancers and in helping to save more lives.

Nick Clegg and Miriam Gonzalez Durantez

# Introduction

Treatment of childhood blood cancers is one of the triumphs of the therapeutic revolution of the last 70 years. It stands alongside other major advances such as the advent of coronary artery bypass surgery, joint replacements and organ transplants.

In 1960, when Bloodwise was founded, a leukaemia diagnosis was an inevitable death sentence.

Only a rudimentary form of chemotherapy was available and this was generally ineffective and caused horrendous side effects. Blood transfusions, painkillers and sometimes antibacterial drugs delayed the inevitable, while the family tried to adjust to the loss of a child – often weighed down by a desperate sense of isolation in the absence of counselling and support.

Now, thanks to research, to which Bloodwise has contributed more than £400 million, at least eight out of ten children with the most common form of the disease survive in the long-term.

## 'Blanket bombing of a target by a blind marksman'

This may sound like a good news story, but it has a very dark side. Internationally acclaimed researcher Professor Mel Greaves, of The Institute of Cancer Research, London, says that treatment is still "very crude".

He compares treatment of children with leukaemia with "blanket bombing of a target by a blind marksman". Therapy still involves toxic side effects – both short and long-term.

For example, Katy Burnett is 24. She has only been in full remission

for seven years and is now being treated for a 'second cancer' arising from treatment for chronic myeloid leukaemia when she was five. There is more about Katy's story below.

This is why we need a kinder cure.

Having to endure three years of chemotherapy would be a harsh treatment for anyone, but more so for a little boy of four like Hugo Griffiths. His nurses wear protective goggles and gloves to administer his drugs because they are so toxic. There is more about Hugo's story below.

Again, this is why we need a kinder cure.

This report is primarily about the scientific quest to improve the lives of children with blood cancer like Katy and Hugo, but it includes their stories and those of other young people and their parents.

It is not easy for parents to reconcile the risks of treatment with the benefits, but children are only experiencing these side and late effects because they are surviving their blood cancers. Radiotherapy, as the main text explains, is now given much less and in much smaller doses, while chemotherapy is also being made less toxic.

## Katy's story

### Living with the complications of treatment – 19 years on

Katy Burnett is 24. Her story is a powerful illustration of the critical need for kinder cures.

Katy developed chronic myeloid leukaemia (CML) at the age of five. Her treatment severely affected her joints and exposed her to the risk of a so-called 'late second cancer'. These can emerge up to 20 years or more after initial treatment.

Katy is now, in the summer of 2017, undergoing gruelling radiotherapy for a 'late second' thyroid cancer.

Her CML emerged during a family holiday in America when her abdomen kept growing and growing... She says: "It was severely distended. I was like a pregnant five-year-old."

Treatment included whole body radiation (the cause of her thyroid cancer) and a bone marrow transplant. Whole body radiation is now rarely used to treat leukaemia, while bone marrow transplants are mainly restricted to children who do not respond to other treatments because they also have their own complications

In 1998 it was a different story. Katy's only chance of survival was a bone marrow transplant within a year of her CML diagnosis. This meant going through all the worry and trauma of finding a bone marrow match.

None of her family were a match. Her family organised a special event, recruiting 80 donors to the Anthony Nolan Bone Marrow Register, but none of them matched Katy. After seven fraught months a Dutch donor provided the life-saving match, but Katy's problems did not end there.



Between 30 and 70% of bone marrow transplant recipients develop graft versus host disease (GvHD) in which the donor's cells treat the recipient's cells as foreign and attack them. Katy was one of them. The disease affected her limbs.

Katy, who has only been in full remission from CML for seven years, recalls having to sit on a bench alone during primary school assembly because she couldn't sit cross-legged on the floor with fellow pupils.

She says: "Even now I don't have the flexibility in my wrists to be able to put my palms flat on a wall or the strength in my hands to squeeze the brakes on a bicycle. It affects my whole body – all the shock absorbers in my joints or muscles – so I can't do any high impact exercise."

But Katy, who is extremely resilient and who is about to start a new fundraising job at Southampton University, still enjoys skiing and dancing. She is, she says, determined to lead a normal life.

# Bloodwise

There are hundreds of cancer charities in the UK, but Bloodwise is the specialist in blood cancer research.

This specialist status is critical. First because it allows a real focus on the specific challenges faced by people living with blood cancer and the doctors, called haematologists, that treat them. And second because childhood blood cancers are classified as 'rare' – and the rarer a cancer, the harder it is to attract funds for research.

Dr Steve Daw, consultant paediatric and adolescent haemato-oncologist at University College Hospital, London, and a national clinical trial coordinator, says: "There aren't many options to raise money for clinical trials in childhood blood cancers. This is what makes Bloodwise so important."

Although childhood cancers are 'rare', they are still the biggest cause of death by disease among children. Moreover, leukaemia, a blood cancer, is the most common childhood cancer, accounting for 30% of childhood cancers in Europe, according to the World Health Organisation.

Rare cancers are often associated with late or incorrect diagnoses; lack of access to appropriate therapies and clinical expertise; very limited numbers of clinical

studies because of the small number of patients and lack of interest in developing new therapies, again because of small numbers of patients.

Despite these formidable barriers, research funded by Bloodwise and others means that a blood cancer diagnosis in a child is no longer an inevitable death sentence. As noted in the introduction, more than eight out of ten children with the most common type of the disease now survive in the long-term.

Incidentally, although around 38,000 people are diagnosed with blood cancer in the UK every year, there are over 100 different kinds of blood cancer. This means that individually even the most common blood cancers are rare diseases. But there is much to learn from common strands between blood cancers, underlining the importance of taking a holistic approach to research.

## Specialist research training

Bloodwise had the foresight in the 1970s to start funding the research training of the brightest young doctors and scientists. In the 1990s it also started

supporting talented science graduates. The result today is a close community of world class experts.

Professor Pamela Kearns, of Birmingham Children's Hospital, who was supported by Bloodwise when she started her career in haematology, has praised the charity for hugely accelerating "the delivery of successful treatments we see today."

## Trial funding

Professor Kearns has made a major contribution to the landmark UKALL clinical trial programme which has helped to increase the number of children who survive acute lymphoblastic leukaemia (ALL). Most if not all children with ALL in the UK are entered in these trials, ensuring that they have access to advances in treatment and that the same high standards in care are consistent for all children across the UK.

## Information for parents and patients

When David and Hilda Eastwood founded the forerunner charity to Bloodwise on Teeside in 1960, little information about blood cancer – to their immense frustration – was available to either people affected by the disease or their families. (There is more about the Eastwood family and the launch of Bloodwise on page 43).

In the Eastwood's era healthcare professionals assumed that too much medical information, especially about treatment side-effects, caused anxiety. But the reverse was later found to be true. For example, research has shown that the more information surgical patients have, the less likely they are to have post operative complications. In radiotherapy greater knowledge is associated with less distress. Information also helps parents with sick children.

Each year Bloodwise sends out about 56,000 free booklets. Available either in print or online, the 22 free titles include *Acute lymphoblastic leukaemia (ALL) in children and young adults* and *Acute myeloid leukaemia in children and young adults up to 16 years*.

All information is written or vetted by medical experts; reviewed by patients and carers; and accredited by the NHS kite mark for patient information, The Information Standard.

## Contact and support

Bloodwise handle about 1,000 support contacts each year via either phone or email and offer peer-to-peer support via blogs and social media. It also runs a patient ambassador programme and helps patients of all ages, their families and other carers.

Ms Donna Dunn is still in touch with Bloodwise following the death in March 2016 of her daughter, Emily Clark, 18, from complications arising from her treatment for Burkitt lymphoma. (See Emily's story below).

She says: "Bloodwise has been phenomenal. They were always there when we needed help and support. There was always someone I could ring up. More than that, they always rang to see how I was. This didn't stop when Emily died. They still ring to ask how we are and whether or not we still want to be involved. This is important to all of us because although we lost Emily, she is still a part of our lives and will be, forever.

"Bloodwise is now also a part of our lives. It helps us to campaign in Emily's memory and this gives us some peace."

# What is blood cancer?

Cancer is mainly a disease of middle and old age. But blood cancers do not discriminate between adults and children and virtually all of them have unknown causes.

There are more than 100 different types of blood cancers and related disorders, according to the World Health Organisation – some of which not even specialist doctors see, they are so rare.

Most blood cancers begin in the bone marrow where so-called stem cells produce three types of blood cells: red blood cells, white blood cells, or platelets. Blood cancers interrupt normal cell development, generating uncontrolled growth of abnormal cells. These cancerous cells can also stop blood from performing its normal functions, like fighting infections or preventing serious bleeding.

Two main types of blood cancers affect children:

Leukaemia is primarily a disease of the bone marrow in children. It is normally ‘acute’ – it results in rapid uncontrolled growth of abnormal white blood cells crowding out normal cells.

Lymphoma is the uncontrolled growth of white blood cells in lymph glands.

## Leukaemia

- Leukaemia (Greek: white blood), is the most common form of childhood cancer.
- It accounts for 30% of all cancers in children under 15.

(All figures are for the UK)

- Acute lymphoblastic leukaemia (ALL) is the most common form of childhood leukaemia.
- Around 400 children, more than half under five, are diagnosed with ALL each year.
- ALL is the only leukaemia – and one of the few forms of cancer – that is more common in children than in adults.
- Around 100 children a year are diagnosed with acute myeloid leukaemia (AML).
- Around 10 babies a year are diagnosed with infant ALL, an aggressive form of the disease.

## Lymphoma

- Lymphoma is the third most common form of childhood cancer.
- There are two main types of lymphomas: Hodgkin (HL) and non-Hodgkin (NHL).
- Around 80 children of all ages are diagnosed with non-Hodgkin lymphoma each year. The condition is more common in boys than girls.
- Around 70 children aged 0-14 years, 120 young people aged between 15-19 years, and 180 between 20-24 years are diagnosed with Hodgkin lymphoma each year.

# Hugo's story

## What-if-itis

A kinder cure for childhood blood cancers would reduce the immense impact of what Lisa Griffiths calls ‘what if’. ‘What-if-itis’ is a cruel manifestation of the inevitable extreme worry.

Her son Hugo, four, has acute lymphoblastic leukaemia (ALL), the most common form of childhood leukaemia. He is in his third year of treatment, meaning that he has spent more than half his life receiving chemotherapy.

When Hugo began his ‘maintenance’ treatment, which helps initial treatment succeed in the long term, the family knew that there would be hospital admissions; that intravenous antibiotics would be administered in hospital and that his low immunity would expose him to infection. It wasn’t a case of if, but of when.

She says: “We were prepared. A bag always packed ready to go, never too far from the hospital, our working life structured so someone was always close to Hugo, just in case. We kept a close eye on him for any signs of infection. We watched and waited.

“As time passed I worried, strangely perhaps, about his lack of infection. How would his body learn to fight if it didn’t get tested?”

A chest infection then meant four days in hospital and a sharp jolt about just how ill Hugo was. His parents watched as his temperature refused to go down. He could barely keep his eyes open or eat anything. Finally he improved, returning home weak and wobbly before slowly bouncing back to health.

It is in more ‘normal’ times such as this – which all parents yearn for – that ‘what-if-itis’ may strike.



Ms Griffiths explains: “When Hugo was first in hospital, it was as if every minute was taken up with medical procedures, with absorbing information, with medication and blood and platelet transfusions.

“At home, I have the chance to breathe, so to speak, to step back and to think, which is always dangerous. I find my mind starting to drift, to think what if?

“What if Hugo is the one that doesn’t make it?

“What if today is wonderful, but tomorrow sees Hugo’s temperature spike and fighting for his life?

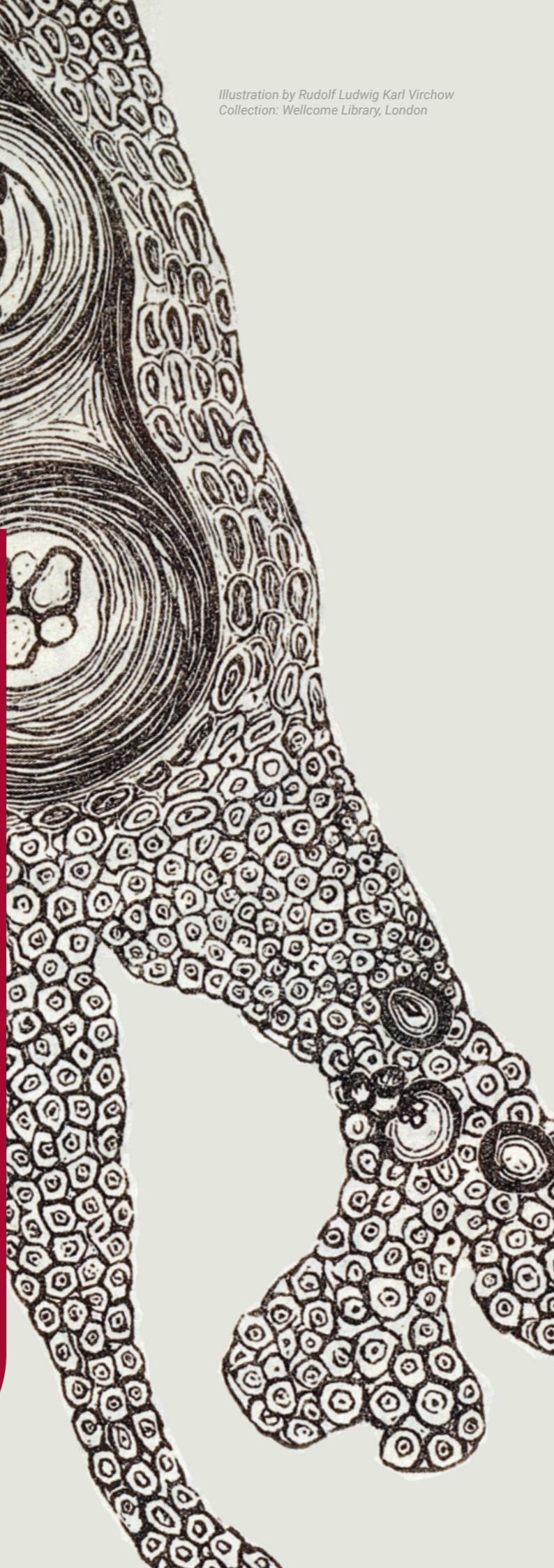
“What if he reacts badly to the next new drug, or the side-effects are too much for his little body to handle?”

## In the beginning

Headlines announcing major advances in medical research sometimes give the impression that progress is rapid. The reverse is usually true. Medical research is far more drip-drip than bang-bang.

The first recorded case of leukaemia was observed more than 150 years ago when a young German doctor, Rudolf Virchow, observed a patient with a large spleen and excessive numbers of white blood cells and very few red ones.

He described it in a medical journal as a case of "white blood" and thought that it was a new disease. Senior colleagues were not convinced and attributed the patient's fatal condition to an infection. But some ten years later, after studying more cases, he published a monograph, including detailed hand drawings, of what he now called "leukaemia," Greek for white blood. His theory about the cause of the disease was essentially correct.



## Unravelling the cause of blood cancers

Establishing the cause of blood cancers is the key to identifying targets for new treatments.

Professor Mel Greaves, of The Institute of Cancer Research, London, has dedicated his career to investigating causes of childhood leukaemia by examining the genetic influences and biological pathways associated with the disease.

In one of the biggest advances, a team led by Professor Greaves and Professor Tariq Enver, then at Oxford University, now at University College London, identified the cancer stem cells that cause acute lymphoblastic leukaemia (ALL), the most common form of childhood leukaemia.

Their discovery arose from research with identical twins Olivia and Isabella, from Bromley, Kent. The two girls gave the Bloodwise-funded scientists an astonishing insight into the nature of leukaemia because of the highly unusual situation whereby both of them were at risk from the disease, but only Olivia developed it.

Published in the journal *Science*, the research showed that in the case of these twins, the first stage of ALL was caused by the merging of two genes known as TEL and AML-1, which occurred in one of the twins in the womb during pregnancy. The genetic change was passed on to the other twin via the circulating blood cells through the placenta, and both twins were born with the genetic change present in their blood stem cells in the bone marrow.

The mutation must have occurred in the womb because neither of the twin's parents had the same mutation. However, only Olivia went on to develop leukaemia because she was unfortunate enough to have suffered a second genetic change after birth, which triggered the onset of the disease.

But what triggered this second mutation? Professor Greaves believes it could have been something as mundane as a common infection.



**"At the time I was first confronted, in a London children's hospital with pale and bald 2 to 5 year-olds, my own son and daughter were of the same age. Children at that age are very special indeed and it was impossible not to imagine, if only fleetingly, your own family in the same position."**

Professor Mel Greaves is one of the world's foremost cancer research scientists. He has worked at The Institute of Cancer Research since 1984, when he joined to establish the UK's first Leukaemia Research Fund Centre (for Cell and Molecular Biology).

His theory is based on the idea that our immune systems may not adapt properly to modern life. Improved hygiene and small family size means that infants are not exposed to infection as they once were.

He says: "The human immune system is extraordinarily dynamic. Rather like the brain, it is not hard-wired, but learns by experience in early life. Paradoxically, it actually needs infection to set it for proper functions and, if deprived of these 'priming' exposures, it malfunctions.

"Survivors of past infectious plagues were almost certainly

the accidental beneficiaries of more potent anti-infection responses. So imagine now a Victorian slum dwelling is transported by a Tardis to a 21st century Western society suburb.

"Where are the necessary infections? Largely eradicated of course. And with some considerable benefit since infant and childhood mortality from infectious causes has declined dramatically. But maybe at a cost. A poorly primed immune system can react inappropriately later, when, say, children mix with their peers at school and inevitably share common infections.

"Triggering leukaemia via an unregulated immune response in susceptible individuals could, I suspect, be one such consequence."

This interesting idea is being investigated by a number of research groups around the world. Professor Greaves is now seeking more evidence to support the 'delayed infection' hypothesis. He says: "I am shortly planning to publish a review summarising all the evidence. What is missing is information on what I call 'common infections'. What are the infections that seem to protect and build up the immune system in the first year of life?

"Are they well known common infections? We just don't know."

Meanwhile, Professor Tariq Enver, now Director of the University College London Cancer Institute, has also built on the twin discovery. He notes that only about 1 in every 100 children born with the initiating mutation seen in the twins goes on to develop leukaemia.

And the way that ALL develops in children is different to adults. Together, this suggests that there is a window of opportunity for childhood leukaemia to develop in early life that changes and eventually closes.

His laboratory is working to systematically define the pattern of genetic mutations in childhood leukaemia characterized by the TEL-AML1 gene fusion, and the cells they occur in – knowledge that is fundamental to improving treatment.

He says: "While survival rates in childhood ALL are relatively good, the life-long side effects of cytotoxic chemotherapy can be severe, and relapsed childhood ALL remains difficult to treat. Through our research, we hope to illuminate new avenues for targeted therapies."

As well as helping children who don't respond well to current treatments, this work may ultimately help scientists to think about how to develop targeted therapies that stop leukaemia developing in the first place, in children who start life at higher risk of developing the condition.

## Olivia's story

Olivia, who was diagnosed with ALL at the age of two and a half, was one of the identical twins investigated by Professors Mel Greaves and Tariq Enver in landmark research. (See page 13)

She is also another patient who illustrates the need for kinder treatments for childhood cancers. During her therapy she developed an attack of chicken pox and lost the sight of one eye.

In his book, *White Blood: Personal journeys with childhood leukaemia*, Professor Greaves says that her sight loss was "almost certainly a consequence of the immunosuppressive impact of drugs given to combat the leukaemia – a tragic but not uncommon consequence of 'collateral damage' of non-specific or toxic drugs."

In a BBC1 programme about childhood leukaemia, the twins' father, recalled how Olivia's loss of sight had shocked and upset him almost as much as the leukaemia itself.

# Clinical trials

Clinical trials compare diagnostic techniques and treatments, mostly drugs, to find out if new ones, or new treatment combinations, are better or safer than existing or standard ones. They are the only rational way to develop new ways to treat children with blood cancer.

The previously mentioned national UKALL trials began in the 1970s and test the latest developments in the diagnosis and treatment of children with leukaemia. Bloodwise, in partnership with Children with Cancer UK, is funding the current UKALL trial, which began in 2011.

These trials have been crucial in increasing the long-term survival of children with ALL in the UK from around four in ten in the 1970s to more than eight children in ten today.

The results of the UKALL 2003 trial highlight the overwhelming importance of the UKALL programme. This trial was designed to evaluate a 'Minimal Residual Disease' (MRD) test, which can detect if there are any leukaemia cells left after initial treatment. It tells doctors how likely children are to relapse. This means that children who are in danger of relapse can be given the high doses of chemotherapy needed to give them the best chances of survival, while other children can be spared unnecessary treatment.

The trial proved that the test is effective. The number of children surviving more than five years

after treatment went up from 85% to more than 91%.

MRD testing is one of the major advances in the treatment of childhood blood cancers and is described in detail later.

## Building on success

The UKALL 2011 trial includes children with ALL, but also includes children with lymphoblastic lymphoma (a type of NHL). The trial is designed to see if using drugs in slightly different ways can achieve the same results but with fewer side effects; and to see if this will also stop the blood cancer from returning.

For example, giving the steroid drug dexamethasone at a higher dose but in a shorter time during introductory treatment may decrease side effects – while giving it at higher dose in later maintenance therapy may help to prevent relapse.

The UKALL 2011 trial ends in January 2018. Meanwhile researchers are planning the sequel – perhaps the most ambitious European trial to date in childhood blood cancer. This will include evaluation of new immune based therapies.

## A future blockbuster

Professor Ajay Vora, chief investigator of UKALL 2011, explains: "Our next trial will be a blockbuster. We'll be collaborating with the Scandinavians, the Dutch, the Belgians, the Portuguese and possibly the French.

"We'll go from recruiting 450 children a year in the UK and Ireland alone to about 1,200 a year."

What is the significance of this near tripling in numbers? Talking on the university website, Professor Pamela Kearns, of University of Birmingham, explains: "Our biggest challenge for children's cancer trials are the small numbers of children involved. This is also a challenge in adult trials in the new era of personalised medicine. The sort of questions we are asking in clinical trials are increasingly focused on small numbers of patients."

A clinical trial may need thousands of patients because sometimes the difference

between two treatments is small. It may take large numbers of patients to find out reliably if one is better than the other. Statisticians give expert guidance to ensure trials have enough people to give reliable results.

Ironically, successful childhood ALL treatment has created a number of problems. More than eight out of ten affected children now achieve a long-term cure, but what about those who relapse? Sadly fewer than six-in-ten survive longer than five years.

Dr Stephen Daw is a consultant paediatric and adolescent haemato-oncologist at the University College London Hospital. He says: "Relapse is a real problem in childhood ALL. The 'salvage rate' in relapsing children is very, very poor. This is one of the main areas where we need something new – a real game-changer."

This game changer could be CAR-T cell therapy – a novel treatment, described later.

## Marathon trials

Why do the individual UK ALL trials take so long? (UKALL 2003 lasted eight years and UKALL 2011 ends in 2018 after seven years.)

- It can take a long time to recruit enough people to take part in a trial, especially in childhood blood cancers where there are limited numbers of patients.
- Treatment of childhood leukaemia lasts a long time – about three years.
- Children need to be followed up for several years to assess survival rates.
- It may be critical to monitor children for a long period to get a reliable picture of the long-term effects of treatment.

# Better tests to tailor treatment

MRD testing: the most important advance in 40 years

The great improvements in treatment of acute lymphoblastic leukaemia (ALL), the most common form of childhood leukaemia, over the last 40 years have not been achieved by new drugs, but by better use of old ones. And better tests have been critical to making that happen.

'Minimal residual disease' (MRD) testing, which measures the amount of residual leukaemia cells in the bone marrow after initial treatment, has been acclaimed as the most important advance in the last 40 years – and a huge step forward in the quest for a kinder cure. It tells doctors what treatment each individual child needs to achieve a cure. This means that today we can give the strongest treatments to those who really need it to survive, and reduce the toxicity of treatment for those who will do well with less, sparing them from the long-term side-effects.

Studied in the UK over 15 years with £3 million of Bloodwise funding and now used around the world, MRD testing has helped to save hundreds of young lives – and should save even more in the future thanks to technological innovations such as next generation sequencing (described below).

It has also enabled many children to side step the terrible side-effects of intensive chemotherapy, with its possible long-term effects on growth, IQ and fertility; and

reduced the amount of time children classified as 'low risk' spend in hospital. The test is used to measure the number of cancer cells left in a child after a month's chemotherapy. At diagnosis a child may have up to one million million leukaemic cells in their blood and bone marrow. After chemotherapy there may still be up to one thousand million cells left.

Professor Ajay Vora, consultant paediatric haematologist at Great Ormond Street Hospital, London, and honorary professor of haematology at Sheffield Children's Hospital, led the pivotal UKALL 2003 clinical trial investigating the potential of MRD testing to tailor the intensity of chemotherapy.

"MRD based refinements in treatment have enabled some 92 to 93% of children with ALL to be cured, but at a price measured in acute (immediate) and late side effects and in the burden to the family and society at large."

So MRD testing is a big step forward, but can still be improved to tailor treatment still more

accurately. "One way we can address this problem is to use more sensitive techniques, such as next generation sequencing. This may help us to identify patients who need even less intensive treatment."

The emphasis in treating ALL has been on aggressive regimes – and in terms of extending survival, achieving a cure and reducing the amount of toxic treatment children receive – it has been a resounding success.

But a lot more needs to be done. The new technologies, it is hoped, will mean a more softly softly approach – a kinder approach – based on the 'less is more' mantra.

Professor Vora says: "The future will be about combining next generation sequencing and genetic approaches. We've already started doing this in a modest way. We now have to think that less treatment might be better. This is in some ways counter to our traditional mindset of more treatment is better."

Dr Nick Goulden played a major role in developing MRD testing at Great Ormond Street Hospital.



## Jack's story

Jack Burnett was one of 2,000 children MRD tested during the trial that established the test as a mainstay in childhood ALL treatment.

His mother Erica recalls: "When Jack was diagnosed, his blood contained 97% leukaemia cells and he was immediately placed on extremely aggressive chemotherapy. During his initial treatment Jack refused to talk, walk and even see visitors. He would beg us to make them stop the treatment. It was a living nightmare."

Jack's MRD test after one month's chemotherapy showed that he was at 'low risk' of relapse. This meant that he had less treatment – which was easier to tolerate.

# Journeys into inner space:

## the genetic revolution

The previous section noted that great improvements in the treatment of ALL over the last 40 years have not been achieved by new drugs, but by better use of old ones.

This would not have been possible without the huge increases in the understanding of the biology of blood cancers. Knowledge about the cellular changes that characterise blood cancers and what starts and drives them is also helping to develop an exciting range of new treatments.

Christine Harrison, a Bloodwise-funded researcher, is Professor of Childhood Cancer Cytogenetics at Newcastle University. Cytogenetics is the study of chromosomes, of which there are 23 pairs containing genetic instructions. In cancer, chromosomes can become rearranged either as the cause of or as a result of the disease.

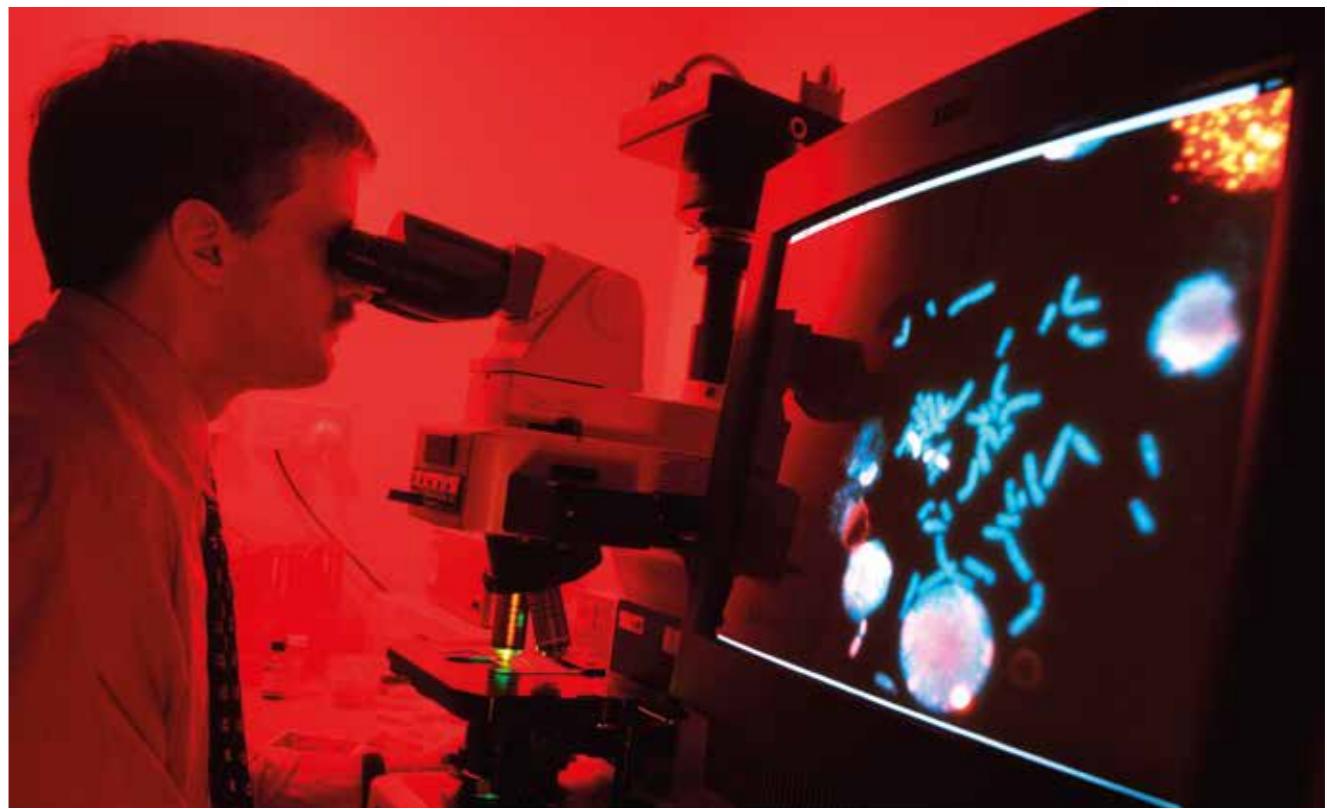
Cytogenetics has been the most powerful tool to date in the risk stratification of blood cancer patients and Professor Harrison has been at the international forefront in advancing the discipline.

### A 75% reduction in the chance of cancer recurring

A pioneering genetic study in Newcastle, funded by Bloodwise, means that children with a rare sub-type of leukaemia now have a 75% lower chance of their cancer recurring.

This abnormality, a genetic error known as iAMP21, occurs when parts of chromosome 21 are copied and shuffled around, resulting in extra copies of some genes and loss of others. This research revealed that this abnormality occurred in about 2% of children diagnosed with ALL. And when researchers looked to see how children who have this genetic change responded to treatment, they found that they were at a much greater chance of relapse.

The team tracked the progress of patients with iAMP21 using samples from clinical trials between 1997 and 2002. They found that more than 80% of children with iAMP21 had relapsed, compared to less than 25% of the children with ALL overall. The long-term survival for the iAMP21 patients was also much lower.



Geneticist analysing human chromosomes by fluorescent microscopy. DAVID PARKER/SCIENCE PHOTO LIBRARY

### A powerful FISH

Bone marrow samples from every child diagnosed with ALL are now tested for the presence of iAMP21 with a technique called 'fluorescence in situ hybridisation' (FISH) which binds glowing tags to DNA to light up the abnormal sequence.

Children with iAMP21 registered on the UKALL 2003 trial were immediately recommended for intensive treatment. The results of this trial were an enormous success, showing that affected children had a dramatically reduced chance of relapse, and that the proportion surviving five years or more had risen to nearly 90%.

Anthony Moorman, Professor of Genetic Epidemiology at Newcastle University, who works alongside Professor Harrison, said that although using the presence of genetic abnormalities to guide treatment was not new within childhood leukaemia,

such a clear demonstration of its beneficial impact on survival was ground-breaking.

Professor Harrison said: "Haematologists worldwide are now treating iAMP21 patients as high risk. We are continuing our research into how this unusual chromosomal abnormality arises in order to develop new drugs that target iAMP21."

By targeting specific cancer pathways, it may be possible to spare children with this form of ALL from the nasty effects of the intensive chemotherapy currently needed to give them a chance of survival.

### CellBank: a life saving treasure trove

The Newcastle team studied the iAMP21 status of children from clinical trials between 1997 and 2002 with samples stored at CellBank – a unique UK initiative funded by Bloodwise and used by researchers from all over the world.



Without CellBank many children with the iAMP21 abnormality would not have survived as the Newcastle team would have been unable to carry out its pioneering research. CellBank contains more than 85,000 samples of biological material from more than 7,000 children with leukaemia.

It evolved from the need to store samples for further research from the UKALL 2003 trial and is now also storing material from the ongoing childhood ALL trial (UKALL 2011); from children with acute myeloid leukaemia (AML); and rarer childhood leukemias such as juvenile myelomonocytic leukaemia (JMML) and myelodysplastic syndrome (MDS); from children who relapse; and from population studies to determine areas of genetic risk for developing childhood ALL.

CellBank also covers most other British children with blood cancer, irrespective of whether or not they are in clinical trials, usually with samples at diagnosis, relapse and follow-up, with linked key demographic and disease information.

Since 2007, CellBank has released samples for 40 national and international studies, resulting in huge global improvements for children living with blood cancer.

### Gene sequencing

Genes and their abnormalities are vital to the understanding of cancer. It is of fundamental importance to know what genetic changes we have in which genes, how many there are and where they are

located within the genome. Advances in sequencing in the 21st century are among the most spectacular in science and have evolved from the work of scientists such as Frederick Sanger.

A British biochemist Professor Sanger invented a method for reading the letters of the genetic code. He was the first scientist to decode the complete genome of any organism and his approach increased by a thousand times the rate at which scientists can sequence DNA. Modern techniques have streamlined sequencing techniques still further, supporting the development of kinder treatments for blood cancers in the future.

Professor Harrison said: "What sequencing has done is to identify a whole range of abnormalities that we were unable to see previously. It's excellent for the detection of chromosomal re-arrangements which may not be visible by looking down a microscope at the chromosomes. For example, if you are reading a sequence and you come across something unexpected, it can indicate a re-arrangement – such as a translocation, a portion of DNA moved from one chromosome to another."

"Targeted sequencing has become a very critical part of our work. You have a target that covers all the regions of the genome where the important abnormalities are located and using this approach you can screen them very rapidly. A typical targeted sequence may involve looking for abnormalities among 80 genes that we know have an impact on survival in childhood ALL."

## Emily's story

### Fatal complications of treatment

Welsh A' Level student Emily Clark was successfully treated for Burkitt lymphoma at the age of 16 even though her tumour was so aggressive that her mother was offered a police escort to rush her to hospital.

After three months in hospital – where she wrote a highly acclaimed blog: *Remission Possible* – she was cancer-free and back at school. Six months later she relapsed and had a bone marrow transplant. Fourteen months later, in March 2016, she died, not from cancer, but from complications arising from her cancer treatment.

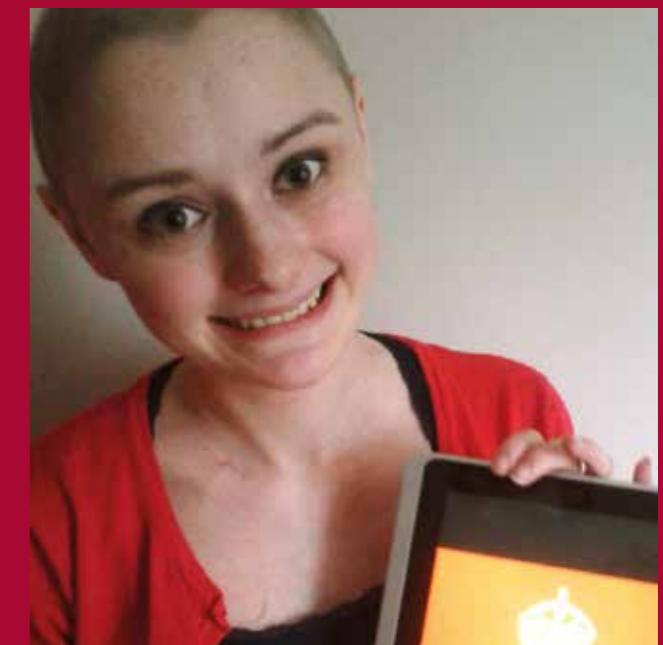
Emily's mother, Donna Dunn, said: "Most people assume that that all we need to do is to cure cancer. This is not enough. We need kinder treatments and kinder cures.

"Emily spent about 300 days in hospital. There's a popular idea that once a cancer patient is in remission, they are better – fully recovered. People said to Emily: 'You've done the hard bit. You're in remission now.'

"But after all her time in hospital she'd become almost institutionalised and there were unexpected problems. For example, the chemotherapy damaged her feet. She had an awful lot of recovering to do."

Like Katy in the previous case history, Emily developed graft versus host disease. But Emily had an additional problem: CMV (cytomegalovirus) infection.

Between 50 and 80% of UK adults are estimated to be CMV carriers. In most people CMV remains inactive –



but in transplant recipients it can flare out of control, resulting in fever, swollen glands or hepatitis (liver inflammation).

Ms Dunn explained: "We were unlucky because both Emily and her Spanish bone marrow donor were CMV carriers. But we had only one suitable donor worldwide. Tragically Emily couldn't fight both CMV and graft versus host disease"

She is immensely proud of Emily because Emily is still saving lives – thanks to her blog appeals which have encouraged thousands of people to join the Anthony Nolan Bone Marrow Register.

She added: "To date, we've had 15 matches thanks to Emily – that could be 15 lives saved".

Ms Dunn hopes that anyone Emily helps to save will have access to the type of kinder treatment that Bloodwise funded researchers are seeking.

# Treatment side effects

We spoke earlier about the need to reconcile the risks and benefits of treatment. The long list of side effects below show how formidable this challenge is. Doctors treating childhood blood cancer want to achieve maximum therapeutic effect with minimum side effects.

If your child has blood cancer, it is important to recognise that although there are many short and long term effects many are rare and your child's personal treatment may be relatively trouble-free. Your child will almost certainly be enrolled into a clinical trial where their response to treatment will be closely monitored. But side effects are one of the biggest challenges for research.

## Physical effects

Child leukaemia and lymphoma patients may be at risk of fatigue, growth delays, cardiac problems, hearing loss, cataracts or lacrimal gland (tears) dysfunction, respiratory problems, dental problems, peripheral neuropathy (numbness or pins and needles in the hands and feet), kidney problems, skin problems, thyroid dysfunction, fertility or pregnancy difficulties and secondary cancers.

## Cognitive effects

Treatments can affect thinking, memory and fine motor coordination. The British Childhood Cancer Survivor Study (BCCSS) reported that childhood cancer survivors fare less well academically than other children.

## Psychological effects

Most childhood cancer survivors are psychologically healthy, but a small number of leukaemia and lymphoma survivors are more likely to report changes in mood, feelings or behaviour, including depression, according to research. The BCCSS reported that childhood cancer survivors were less likely to marry than the general population.

## Drugs

- Several different types of drugs are used to treat childhood leukaemia and lymphoma. Alkylating drugs (such as cyclophosphamide, procarbazine, carmustine and cisplatin – types of chemotherapy) are linked with heart and lung problems, low testosterone and sperm counts in boys and premature ovarian failure in girls and secondary cancers, particularly acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS).
- High dose and long-term use of anthracyclines, another type of chemotherapy, may cause heart muscle injury and heart failure. These drugs treat childhood AML, ALL and Hodgkin and non-Hodgkin lymphoma.
- Children may be less able than adults to tolerate multiple chemotherapy, particularly when combined with radiotherapy.
- Bleomycin is an antibiotic that is poisonous to cancer cells for lymphoma, and is toxic to the lungs and may cause adult respiratory distress syndrome and lung failure.
- Corticosteroids are linked with osteoporosis and cataracts. High doses can cause long term hip damage.
- DNA repair inhibitors such as etoposide can cause AML.
- Drugs such as vincristine or vinblastine that prevent cancer cells from dividing can cause peripheral neuropathy. These drugs are used to treat most blood cancers.
- Methotrexate, a leukaemia and lymphoma treatment, is associated with osteoporosis and lung damage.
- Total body irradiation, once routine in stem cell transplantation, can cause many late effects. It is now not routinely given to children.
- BCCSS research found that girls with Hodgkin lymphoma irradiated with radiotherapy above the diaphragm were at increased risk of developing breast cancer later in life – 13 times higher than the general population.

## Radiotherapy

- Radiotherapy to the head and neck is associated with learning difficulties, growth hormone deficiency, hypo or hyper thyroidism, hearing loss, vision problems such as cataracts or glaucoma, dental problems, brain or thyroid cancer and osteoporosis. Occasionally puberty may be premature or delayed.

# Kinder treatments for children with lymphomas

The UK arm of the EuroNet PHL-C2 trial will be launched in 2017 to refine first-line treatment for children, adolescents and young adults (up to 25 years of age) with Hodgkin lymphoma. It is designed to see if it is possible to reduce radiotherapy treatment and to see if a novel combination chemotherapy regime will compensate for the reduction.

Radiotherapy is the main cause of long-term effects in younger people and the trial seeks to maintain high cure rates while using radiotherapy only in a small minority of patients.

Dr Stephen Daw, Consultant Paediatric and Adolescent Haemato-Oncologist at University College London Hospital, explains: "People sometimes describe Hodgkin's in young people as having a perfect storm of late effects because the cure rates are very high and because the patients are young, with a long life ahead of them – during which time they may accumulate more and more late effects of treatment.

"So, for example, if you have radiotherapy in the neck, you may be at risk from a stroke in later life. If you have radiotherapy in the chest and it affects the heart, you may be at increased risk of cardiovascular disease.

"These side effects may come on after 10 or 20 years – which for a young patient may mean they are still only in their 30s or 40s. This is why reduction in radiotherapy

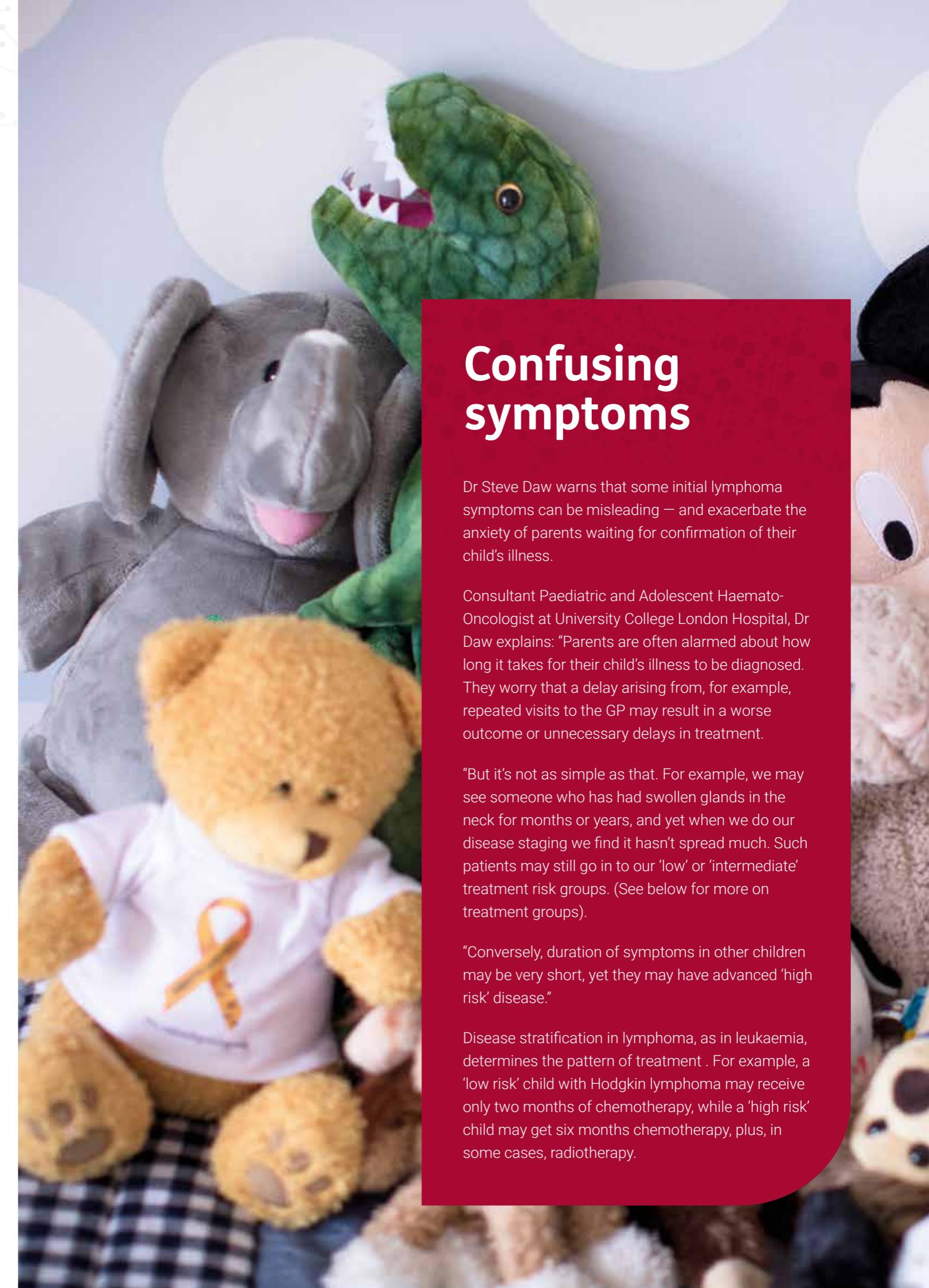
is so critical. If you're 55 or 60 when you have radiotherapy, you may be 80 before any long-term effects strike.

"People now talk about cancer being a chronic disease, but in children and young people, our aim is to find a cure so the treatment is over but without severe later effects.

"Treatment is intensive with lots of side effects, but it's not long. We're only reducing treatment in patients where we think we can get away with it because we don't want to put young patients at too much risk of recurrence which would mean having to go through 'salvage treatment'. (Treatment after disease recurrence).

"Across the board we're aiming for cure rates of about 90% in children and young people. So only about 10% need salvage treatment."

Salvage treatment still cures most patients with Hodgkin lymphoma, but involves the burden of additional high dose treatment and often a stem cell transplant.



## Confusing symptoms

Dr Steve Daw warns that some initial lymphoma symptoms can be misleading – and exacerbate the anxiety of parents waiting for confirmation of their child's illness.

Consultant Paediatric and Adolescent Haemato-Oncologist at University College London Hospital, Dr Daw explains: "Parents are often alarmed about how long it takes for their child's illness to be diagnosed. They worry that a delay arising from, for example, repeated visits to the GP may result in a worse outcome or unnecessary delays in treatment.

"But it's not as simple as that. For example, we may see someone who has had swollen glands in the neck for months or years, and yet when we do our disease staging we find it hasn't spread much. Such patients may still go in to our 'low' or 'intermediate' treatment risk groups. (See below for more on treatment groups).

"Conversely, duration of symptoms in other children may be very short, yet they may have advanced 'high risk' disease."

Disease stratification in lymphoma, as in leukaemia, determines the pattern of treatment. For example, a 'low risk' child with Hodgkin lymphoma may receive only two months of chemotherapy, while a 'high risk' child may get six months chemotherapy, plus, in some cases, radiotherapy.

# Preventing future sterility in young children

Clinical trials have provided the evidence to challenge and improve standard medical practice, creating a cycle of continuous improvements in treatment and outcomes for patients. For instance, proving that the drug procarbazine given for Hodgkin lymphoma caused sterility in boys.

Early results in the 14 country EuroNet-PHL-C1 trial showed that another medicine in the same 'drug family', dacarbazine, worked just as well without affecting fertility.

The trial was the forerunner to the EuroNet PHL-C2, reported above. Its primary aims were to find a new combination chemotherapy using dacarbazine instead of procarbazine and so reduces infertility. The trial also wanted to see if chemotherapy alone was as good as chemotherapy and radiotherapy for children and young people with Hodgkin lymphoma who had had a good response to chemotherapy.

Radiotherapy was omitted in half the patients without any drop in the cure rates. Again the results successfully challenged what many physicians regarded as standard care and this change should reduce the number of 'second cancers' in future patients.

Hamish Wallace, Professor of Paediatric Oncology, University of Edinburgh & Royal Hospital for Sick Children says: "We haven't published the results yet, but we've presented the data all over the world. It shows that we can maintain excellent survival in more than 90% of our patients without radiotherapy if they have a good response to treatment.

"It's also very exciting that we can avoid using procarbazine in boys so that their fertility is now not affected and this is a big improvement which could only be achieved in a clinical trial."

The children and young people in the trial were all under 18 and divided into three groups according to the severity of their disease. The greater the risk, the more likely they were to have radiotherapy.

Although the EuroNet-PHL-C1 trial has been acclaimed a success, it highlights the need for novel treatments for children who do not respond to therapy or who relapse.

# Hard to treat childhood cancers

## Infant acute lymphoblastic leukaemia (ALL)

Infant ALL in babies under one year of age is exceptionally rare, with only 10 or so cases a year in the UK. It is also highly aggressive. Only four out of ten affected babies are likely to live for more than five years.

Currently, the only way to treat infant ALL effectively is with an aggressive approach, in most cases with chemotherapy and bone marrow transplantation. Young babies, whose fragile bodies at diagnosis are often overwhelmed by leukaemic cells, are especially susceptible to the strains these therapies place on them. Many are not strong enough to tolerate the treatment that might save them. There is no greater need in childhood blood cancers for a kinder cure.

Dr Anindita Roy, Clinician Scientist at University of Oxford and Honorary Clinical Lecturer in Paediatric Haematology at Great Ormond Street Hospital, London, is trying to track the origins and development of infant ALL. Her work is also furthering understanding of childhood ALL, the most common childhood cancer.

Research has established that many childhood leukaemias originate in the womb. Immature blood cells in the foetus, so-called progenitor cells, develop mutations in which genes are re-arranged or moved. This makes them more susceptible to events after birth that turn them into rapidly proliferating leukaemic cells.

This second 'hit' or development, which triggers childhood ALL, may happen many months or years after birth, perhaps as a result of infection or an abnormal immune response.

## A unique disease

Dr Roy says: "What makes infant ALL unique is that it doesn't need this second hit."

In 70 - 80% of cases, infant ALL is associated with the abnormalities/rearrangements of the MLL gene (mixed lineage leukaemia).

Dr Roy explains: "These babies develop the MLL gene re-arrangement before birth – and that's enough to cause an aggressive leukaemia. That's why infant ALL develops so quickly. It doesn't need the second hit that characterises childhood ALL."

"Our most interesting finding is that we have identified a unique foetal progenitor cell that we think may be the target cell for the MLL re-arrangement that causes infant ALL."

The next phase of the research will be to try and move towards developing MLL-like disease in an animal model. This could take research a step closer to identifying a target for treatment.

# A new strategy for children whose disease relapses

Fewer than six out of ten children with acute lymphoblastic leukaemia (ALL) whose disease relapses survive longer than five years.

Problems arise when genetic faults within developing white blood cells kick-start and drive leukaemia growth. The types and combinations of genetic errors are known to influence whether a child is likely to respond well to initial treatment. In turn this affects survival chances.

Genetic screening is already used to tailor treatment at diagnosis to ensure the most appropriate level of chemotherapy. But until a recent study at Newcastle University, little was known about how these 'genetic markers' could guide treatment if the leukaemia came back.

Funded by Bloodwise, the Newcastle scientists analysed leukaemia cells from 427 children treated for relapsed ALL between 2003 and 2013.

At the time, in 2016, children with relapsed leukaemia were grouped according to whether they were at a 'standard' or 'high risk' of a poor outcome. These classifications were based on factors such as how long the child had been in remission and if the bone marrow

contained leukaemia cells at the time of relapse.

Treatment for 'high risk' children included gruelling stem cell transplants while those at 'standard risk' tended to have just chemotherapy.

It had been assumed (and this underlines the importance of clinical trials) that those whose leukaemia had returned a long time after treatment had a good chance of survival. These children received less intense chemotherapy than high risk children.

But the Newcastle team, led by Professor Anthony Moorman and Dr Julie Irving, found that the standard risk group who, at the time of relapse, had one or more 'high risk' genetic abnormalities responded poorly to chemotherapy. In addition, they discovered abnormalities in a number of genes (TP53, NR3C1, BTG1 and NRAS) which provided additional information about how and why these children fared poorly.

"The uncertainty of the long-term side effects is certainly difficult to cope with, and has caused me anxiety in the past, but I suppose that these effects have been overshadowed slightly by my recent diagnosis with pulmonary hypertension, which brings with it more present day-to-day effects and poses a greater risk to my health, also eliminating the possibility of having children."

Hannah, who was diagnosed with ALL in 2005 when she was six years old

Professor Moorman said that current methods to guide treatment for relapsed leukaemia had not been good enough, "with some children believed to have a good chance of survival actually responding very poorly to chemotherapy."

Published in the journal *Blood*, the study also provided insights about how to treat children with similar gene defects. For example, children with a defect in one of the so called RAS genes may benefit from a new drug called a 'MEK inhibitor' which kills cells with a faulty RAS gene.

Researchers have developed various drugs that target specific proteins that help cancer cells grow or resist chemotherapy. But some complex proteins have been notoriously hard to block. These include those produced by the RAS genes, a family of three closely related genes. that produce Ras proteins

The Ras proteins are 'molecular switches' inside a cell that, when turned on, activate signalling pathways that promote cell growth and survival. Mutations in RAS genes drive tumour development and progression.

Having failed to design a drug that binds tightly to the Ras proteins, researchers have tried to attack them indirectly, via other proteins in the signalling pathways that Ras proteins regulate. The MEK inhibitor is one such drug.

Julie Irving, Professor of Experimental Pathology at Newcastle University, says: "In terms of novel therapies for relapsed ALL, my group has shown that that mutation of genes activating the RAS/RAF/MEK/ERK pathway is the most common genetic abnormality and have identified MEK inhibitors as a potential novel therapeutic option which would be applicable to around 40% of children."

# CAR-T cell therapy

Researchers and clinicians are traditionally cautious about overstating the potential benefits of novel therapies, but the potential of CAR-T cell therapy for treating relapsed ALL is generating immense scientific excitement. Relapsed ALL is a leading cause of death from childhood blood cancer.

Dr Martin Pule, senior lecturer in Haematology at the University College London Cancer Institute, says: "There are very few examples in modern medicine where you have a treatment, perhaps once in every 20 years or so, where you see this kind of sustained response rate in cancer treatment.

"It's amazing that 95% or more of these children with refractory or relapsed ALL go into remission and two-thirds stay in complete remission." (So called 'refractory' patients do not respond to initial therapy).

"The real success started around 2011. The number of patients treated has risen dramatically over the last few years, so there aren't many people who were treated in 2011, but there are a few, and this is really encouraging."

## T-cells – the workhorses of the immune system

As the name suggests, the driving force of CAR-T cell therapy is the human T-cell. Known as the workhorses of the immune system because of the way they

orchestrate our immune systems, T-cells send chemical instructions (cytokines) to the rest of the immune system to prime the body against invading bacteria, viruses or parasites; recognise and kill virus-infected cells directly and work with B-cells to produce antibodies, the foot soldiers of the immune system.

## A living drug: making CAR-T cells

CAR-T cells originate from the patient's own blood. The T-cells are removed from the blood and genetically engineered to produce receptors on so called chimeric antigen receptors or CARS.

These receptors enable the T-cells to recognise and attach to a specific protein or antigen on cancer cells. The most advanced CAR-T cell therapies target an antigen on B-cells called CD19.

After harvested T-cells have been engineered to express the antigen specific CAR, they are 'expanded' in the laboratory into the hundreds of millions, creating what is, in essence, a living drug.

The CAR-T cells are then infused into the patient in the hope that they will further multiply and, guided by their engineered receptor, seek out and kill cancer cells.

## Seek and destroy

Dr Pule compares the process to a robot going on a seek and destroy mission to target the CD19 antigen on the surface of cancer cells.

It sounds simple and wonderful, but it's anything but. Whereas natural T-cells have been road-tested since antiquity in the trial of evolution, CAR-T cells are in the infancy – and don't always work.

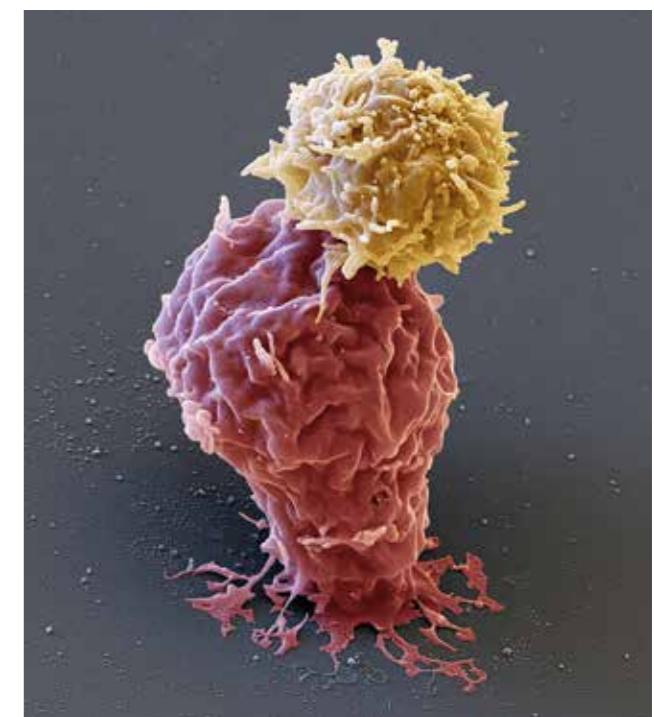
Dr Pule explained: "About a third of rejections occur because CAR-T cells just peter out after a short period of time. We like to see the cells remaining in the patient for six to nine months – any shorter than that and the leukaemia tends to recur."

What about re-treating patients who lose protection?

"That's a good question. It's something people are trying to do now."

Why do CARS disappear? "You're making the CAR-T cells from the patient themselves. Their T-cells may have been battered by chemotherapy. Alternatively, the patient's own immune system may reject the CAR if it has an artificial coating. Early CARS included a mouse antibody. One of our aims is to make CARS as 'human' as possible."

There is a further complication. Leukaemia cells may learn how to stop making the CD19 protein, meaning



Leukaemia cancer cell being attacked by CAR-T cell.  
EYE OF SCIENCE/SCIENCE PHOTO LIBRARY

that the CAR-T cells cannot 'see' their target anymore. Dr Pule says: "This is what cancer does. It mutates, just like infection."

## Side effects

CAR-T cell therapy can cause severe and sometimes fatal side effects. These include cytokine-release syndrome (CRS). Cytokines are chemical messengers that help to generate and direct the immune response. CRS produces a huge and rapid release of cytokines in the blood that can produce big falls in blood pressure and dangerously high fevers. CRS can be managed in many cases with routine support treatment such as steroids.



Dr Pule says: "Doctors are developing extensive expertise in managing these immune syndromes."

## Research

Investigators seeking to increase the numbers of patients who go into sustained complete remission from 60 to 100% are working on developing a CAR-T cell that will target two antigens at the same time – CD19 and CD22.

"It's a common trend in oncology," says Dr. Pule. "You don't try and target one thing. You go for two. The more things you can throw at a leukaemia cell the better. It's not intelligent. It just randomly switches things off. While it may be able to switch off the CD19 antigen, the chances that it can switch off both CD19 and CD22 at the same time is very low."

In another approach the Great Ormond Street Hospital (GOSH) for children in London, one of the world's leading research centres, is testing a gentler CAR designed to stop fragile children's immune systems from 'over-heating' during treatment. The plan is for a model that will activate at a slower rate – more like a crescendo than a big bang – and remain in the patient for longer, with increased therapeutic effect.

GOSH is also carrying out a study designed to help the small proportion of children in whom it is hard to make cells – in particular the very young and those who have had extensive chemotherapy or reacted badly to it. Researchers are exploring the potential of CARS made from unrelated, human donors in a programme involving gene editing.

## Approval of CAR-T therapies and the cost challenge

So how close are CAR-T therapies to entering clinical practice? As this report was being prepared, the first CAR-T therapy for cancer was approved by the US Food and Drug Administration (FDA), (see box).

'CTL019' is a CAR-T therapy that targets CD19, and has been developed by the pharmaceutical company Novartis. It has now been approved in the USA for use in children and young adults with relapsed or refractory B-cell ALL.

But there is much uncertainty about how quickly these therapies will enter normal clinical practice. They require specialist delivery and are likely to be very expensive.

Dr Alasdair Rankin, Director of Research at Bloodwise says: "Many experimental CAR-T therapies appear so compelling that it is inevitable that they will play a significant role in cancer treatment, but this treatment approval is just a first step and we have much, still to learn. This specific treatment for children with B-cell ALL will initially be restricted to children who have no other treatment options.

"The future of CAR-T, for childhood blood cancer and other types of cancer, will depend on long-term data on effectiveness, how far treatment costs can be reduced, and the extent to which other targeted therapies can ultimately achieve similar effects at lower cost."

## Removing the 'spark plug' that drives leukaemia

Imagine a leukaemia cell as being like a car that has run out of control. How would we stop it if we were treating it with a drug? By crashing it – and possibly damaging the bodywork and internal structures. How much simpler and safer it would be if we could just remove the spark plug.

Professor Josef Vormoor, Professor Olaf Heidenreich and colleagues at Newcastle University are trying to develop drugs that would have the same kind of neutralising effect on leukaemia cells as removing a spark plug would have on a moving car. They want to hit leukaemic cells while avoiding healthy infection-fighting cells.

**"I'm often asked whether being a paediatric oncologist is depressing. It isn't, because we can cure two-thirds to 80% of children. That's incredible considering that only a generation ago, the majority of children with cancer died. But children are still dying today. So if I could find a treatment that stopped that, it would be the best thing I could do in my life. But in the end, it doesn't matter who finds a cure — the key thing is that somebody finds it."**

Josef Vormoor, Sir James Spence Professor of Child Health, Northern Institute for Cancer Research and Honorary Consultant in Paediatric Oncology at the Great North Children's Hospital, Newcastle-upon-Tyne.

Professor Vormoor said: "We want to interfere with leukaemia cells more intelligently. If you take acute lymphoblastic leukaemia (ALL), for example, the vast majority of children are cured, but this takes two to three years, with lots of side effects and risk of infection. We want to develop kinder treatments that are not necessarily more effective, but which have fewer side effects."

And treatments that are fast-acting – with the equivalent effect of removing a car spark plug? "It would be great if we could treat leukaemia within, say, two weeks or a month instead of two or three years."

Will this be possible? "It's very hard to predict. There are lots of promising new drugs." But he warned that new treatments may also cause unacceptable side effects and would need extensive testing.

In research to find the leukaemia 'spark plug' the Newcastle team is disabling some 20,000 genes to discover how ALL cells renew. "Once the researchers find out these key genes, they can then look for ways to target them, switching the leukaemia cells off. This is painstaking work, that may open up a much needed new avenue of attack", Professor Vormoor said.

## A historic day

On August 30, 2017, tisagenlecleucel, CTL019 (brand name: Kymriah) became the first CAR-T cell therapy to be licensed by the US Food and Drug Administration. The manufacturers, Novartis, reported that in one study it had achieved an overall remission rate of 83% (52 out of 63 patients).

Novartis plans to apply for EU licences for Kymriah later this year.

The US licence applies to children and young adults aged up to 25 with the most common form of acute lymphoblastic leukaemia (ALL) who have had two or more treatment relapses or who have failed to respond to treatment.

# Dr Alasdair Rankin

Bloodwise's Director of Research talks about priorities in the quest for a kinder cure

**John Illman:** What's the biggest challenge in childhood blood cancer research?

**Dr Alasdair Rankin:** Continuing the progress to make treatments both gentler and more effective. We've taken, for many children, the first critical step of saving their life, the first aim of cancer research. But this is not good enough – we need to save every child's life. And we need to give them the life they would have had without cancer; and to take far less of their life away from them during the treatment process.

It's deeply frustrating to me when people look at the success that research has achieved for children with blood cancer and say: "They've done fantastically well, so let's focus on something else." The reality is that we've started a job that isn't finished. We do not save one child out of five. And the treatments we use to save lives cause children real harm. I just don't think that's acceptable.

**Jl:** I was intrigued to hear that developing blood cancer therapies can be easier than developing therapies for other cancers. Why?

**AR:** By their nature blood cancers are easier to take samples from, to study and are easier to reach with treatments than many cancers. Tumours made up of a big solid mass are more challenging. It's also harder to get the therapy to the site of solid tumour masses.

**Jl:** Blood is very accessible...

**AR:** Yes it is, but it's very easy to be simplistic about this. For example, lymphomas can grow in your lymph nodes and leukaemia can grow in your bone marrow and bits of cancers can hide in our bodies and so treatment needs to access them. But new treatments, such as CAR-T cell therapies, are immune based. They use cells that track through your immune system and so go to places where white blood cells

naturally hide – the type of cell that is affected by blood cancer. (CAR-T cell therapy is discussed on pages 32-34).

**Jl:** How do you evaluate Bloodwise's contribution to blood cancer research?

**AR:** Bloodwise's contribution to this has been fundamental. We've put substantial long-term investment into the fundamental research that drives understanding of blood cancer and development of the genetic tests that have allowed kinder treatments to be developed.

**Jl:** How do you as a father yourself react to the horror of childhood blood cancer?

**AR:** As a research director I've met many parents who lives were profoundly changed when their child was diagnosed with leukaemia. Their stories are as strong an incentive as you can find for funding research to create change. As a parent of young children, I can't help



imagining myself in their position. The thought of not being able to protect your child from something as devastating as leukaemia is just awful.

**Jl:** What's the point of Bloodwise when there are so many other bigger cancer charities?

**AR:** Having a variety of funding sources is important, and several funders have contributed to progress in blood cancer research in the UK. But having a research funder that is dedicated to blood cancer in general and to childhood blood cancers has taken research in the UK to a level that would not have been achieved without Bloodwise. Our prioritisation of blood cancer has allowed excellent scientists to focus careers on these conditions.

And the better they become at what they do with our support, the more funding they have attracted from others to make a difference to people living with blood cancer.

**Jl:** Finally, what are the three biggest contributions that Bloodwise has made to blood cancer research?

**AR:** One: minimal residual disease testing. Two: other genetic tests to help doctors guide the right treatment for the right child at the right time. And three: investing in the people and research infrastructure that have made these discoveries possible, which means that more will follow if we keep pushing forward.

# Future proofing blood cancer research

## A new kind of doctor/scientist for a new kind of medicine

For years blood cancer treatment has been founded on chemotherapy and radiotherapy, treatments that work, albeit all too often with harsh consequences for patients and their families. But recently there has been an increasing emphasis on novel treatments such as CAR-T cell therapy and drugs that attack specific genetic abnormalities.

The change was led by imatinib (brand name Glivec), a drug which had a revolutionary impact on chronic myeloid leukaemia (CML). It targets the BCR-ABL abnormal fusion gene which is formed when pieces of chromosome 9 and 22 break off and trade places. Most people with CML have this mutation – as do about 25% of adults and about 3% of children with acute lymphoblastic leukaemia (ALL). Glivec and newer related drugs are now used extensively to treat ALL.

Genes and genetic abnormalities are, of course, vital to the understanding of cancer and much leukaemia research – in the wake of the discovery of imatinib – is now focused on identifying mutations and developing drugs to target them.

## Precision medicine

Professor Ajay Vora, chief investigator of childhood ALL trials in the UK, believes that understanding the genetic changes that drive childhood blood cancer will have a transformational effect on how we treat the disease. It will also build on the development of risk stratification of young patients into 'low', 'intermediate' and 'high' risk treatment groups.

He says: "There's a lot of talk about precision medicine. Disease stratification is all about precision, but the emphasis now is to target the genetic changes you can see under the microscope. If you have lung cancer with a certain genetic change, and an ovarian cancer with the same genetic change, you can treat them both with the same drug."

"In future people like me will no longer be specialists in certain cancers. I trained as a haematologist to treat all haematological disease, but then my interests narrowed into new ways of treating ALL. I may broaden out again. Rather than being an ALL specialist, I may specialise, for example, in ALK (anaplastic lymphoma kinase) positive cancers which include small cell lung cancer and lymphomas. This is what precision medicine will be all about."

(ALK is a gene that instructs your body how to make proteins that help cells talk to one another. Part of it breaks down in ALK positive cancer and attaches to another gene.)

## Linking the laboratory to the clinic

Christine Harrison, a Bloodwise-funded researcher, is Professor of Childhood Cancer Cytogenetics at Newcastle University. Cytogenetics has been the most powerful tool in risk stratification of disease and she has played a critical part in developing and refining it.

She believes that another decisive factor is also driving research: improved collaboration between the scientist at the laboratory bench and the clinician at the bedside. This encourages a more streamlined translation of laboratory findings to

clinical practice, something called 'translational research'.

Professor Harrison recalls: "When I began my career, it was much more difficult for scientists to communicate with clinicians. As a scientist you had to be very confident if you were proposing any medical changes. Scientists and clinicians now work much more closely together in this new era of translational research."

The concept of translational research emerged in response to concern about the long time lag between scientific discoveries and changes in treatments, practices and health policies to incorporate the newer discoveries.

Translation requires linguists who are fluent in at least two languages and the same may be true of translational medicine in which the clinician-scientist acts as a conduit between the laboratory and the clinic. Dr Anindita Roy, a Bloodwise-funded clinician-scientist in paediatric haematology, is combining clinical work at the Great Ormond Street Hospital for Children in London with

research into infant ALL, a highly aggressive form of the disease.

Dr Roy envisages a front line role for clinician-scientists in the quest for kinder treatments for children with blood cancer. She says: "There's a great need for more clinicians to do science. When I started my training, there weren't many integrated training pathways, but now there are many options to combine academic and clinical training. Even if you don't pursue an academic pathway, I believe that doing some research makes you a better clinician."

## Infinite demand and finite resources

The great optimism in research is tempered by the gulf between infinite demand and finite resources. Hamish Wallace, Professor of Paediatric Oncology, University of Edinburgh & Royal Hospital for Sick Children, strikes a warning note.

He says: "When we take a bit of tumour, we don't just look at it under the microscope. We do lots of genetic testing. The end result is that we identify new types of cancer, but splitting up cancers

into genetic types of more than say six is problematic. The rarity of these cancers means that we'll never be able to do the studies to see if the different molecular signatures are important in terms of prognosis.

"But understanding more about the causes of leukaemia – about individual genetic susceptibility and environmental triggers, which are probably viral – will enable us to at least explore the possibility of vaccination."

In the meantime Professor Vora sees a possible future for so-called re-purposed drugs – old drugs used in new ways. He says: "Take statins, for example. They're now emerging in some re-purposing studies as being of potential benefit in certain types of leukaemia.

"Because they've been used in hundreds of thousands of people, we have a very good idea of their safety profiles. There are at present no clinical studies with statins in leukaemia patients, but there are pre-clinical studies with mice."

Resources may be finite, but the range of possibilities is infinite.

# Collaboration: a key to success

Bloodwise's strength is that it is a specialist charity for blood cancer research and also provides support for patients and their families, but its interests overlap with other specialist charities and fundraising bodies. Collaboration builds on its success.

For example, Bloodwise, in collaboration with Children with Cancer UK, provides funding for the UKALL 2011 trial, one of a series of trials investigating developments in diagnosis and treatment of childhood acute lymphoblastic leukaemia (ALL), the most common childhood cancer.

## Children with Cancer UK

Cliff O'Gorman, of Children with Cancer UK, says: "Collaboration is the key with charities like ours – the only way we are going to save children's lives. We work very closely with Bloodwise, CLIC Sargent and the Great Ormond Street Hospital Charity.

"Having lost a brother and a sister to cancer, I'm not interested in competition, only collaboration."

Paul O'Gorman, 14, died in February 1987, only nine weeks after his leukaemia diagnosis. He asked his parents, Eddie and Marion, to help other children with the disease. His sister Jean started to raise funds, but she too died from cancer, only nine months later, in November.

Just days after her death the family met Diana, the Princess of Wales, who suggested that they should launch a charity – which she inaugurated in January 1988. Its first task was to raise £2 million for a research centre at London's Great Ormond Street Hospital. The Paul O'Gorman Childhood Leukaemia Research Centre opened in 1995 and has built up a reputation for world-class science.

Children with Cancer UK has funded research to the value of more than £10 million in partnership with Bloodwise.

# Hugo's story

## Looking to the future

Earlier, Lisa Griffiths spoke about her fears when her son Hugo, now aged four, was diagnosed with acute lymphoblastic leukaemia (ALL). But how do a mother and father reconcile themselves to the devastating news that their young child has cancer?

Ms Griffiths says: "When Hugo was diagnosed, our lives were literally turned upside down. Panic, fear and the need to hear from somebody, anybody that he will eventually be well again was all consuming, but nobody can give you that answer. Patience takes on a whole new meaning when you're delivered the bombshell that your child has cancer.

"For months this fear was internalised. It had to be. We couldn't show fear in front of the children. We had to be strong. His brother, Henry, was four, just about to start school, a hugely important time in his life and suddenly everything was about Hugo.

"Since Hugo's diagnosis, I have discovered how strong and resilient children are, but I have also imagined my child's funeral. I have thought about what would be said and who would be there. I have questioned whether I would be able to go without Hugo and how losing him will affect Henry, and I know that I am not alone in having these thoughts.

"Without wishing precious time to fly by quickly – the time when your children are young, when they need and love you unconditionally, the time you'll never get back – we're looking forward to September 2018. We're mentally fast-forwarding a whole year to when Hugo's maintenance chemotherapy ends and we can look forward to a little normality again.



"But we're not only raising a child with leukaemia. Hugo now has a disability. The steroids have weakened his muscles so that now he's reliant on a wheelchair. We're facing yet another world of learning and adapting, and with us, big brother Henry is learning too. Too quickly and too starkly for our liking, but he's learning patience in abundance and is growing into a wonderful, kind older brother and role model to Hugo.

"We hope one day to be free from the gnawing anxiety. To be free in a moment that isn't snatched away with the dreaded feeling: 'What if it comes back?'. Hugo will have regular check-ups once his treatment is over and as the time between them grows, we hope our worries will disperse and the nightmare of Hugo's blood cancer will finally be a thing of the past."

# Conclusion

In highlighting the quest for more effective and kinder cures for childhood blood cancers, this report tells the extraordinary story of the risks and benefits of treating children with blood cancer. It is a unique story.

It moves from the formation of Bloodwise in 1960, when a leukaemia diagnosis was an inevitable death sentence, to today when eight out of ten children with the most common form of the disease survive. But treatment involves toxic side effects – both during and after treatment.

How do we reconcile these risks to the benefits of treatment? It is critical to recognise that these side effects only occur because affected children are now living long enough to develop them – secondary cancers, for example, may present 20 years or more after initial treatment.

Parents are inevitably and understandably upset and alarmed to learn that treatments that cure can also harm small, fragile children. Few things are more distressing, but the clinical trials in which most of their

children are enrolled represent state of the art treatment. It should give them the best possible chance of normal life.

Moreover, the therapy is working. Treatment is becoming significantly kinder, gentler and more effective – thanks to research. For example, a drug that was used routinely to treat Hodgkin lymphoma caused sterility in boys. Another drug that does not affect fertility has been found to be just as effective.

Research has also shown that it is possible to treat 90% of Hodgkin lymphoma patients without radiotherapy if they show a good initial response to treatment. Over time this will mean that many hundreds of children will not go on to develop secondary cancers, perhaps 15–20 years after treatment. Whole body radiation, once a source of devastating late effects, is no longer routinely used. Research has shown that it is unnecessary.

Medical research is synonymous with drug development, but there has been a conspicuous lack of new drugs for childhood blood

cancers over the last 40 years. The spectacular progress is partly attributable to research showing how to make better use of existing drugs by prescribing them in combinations and varying dosage and duration of treatment.

But so called CAR-T cell therapy, a novel treatment based on T-cells from the patient's own blood, is generating immense excitement. T-cells are white blood cells within the immune system. As Dr Martin Pule, Senior Lecturer in Haematology, University College London, observes in the report: "There are very few examples in modern medicine, perhaps once in every 20 years or so, where you see this kind of sustained response rate in cancer treatment."

Again, CAR-T cell therapy is the product of research which adds substance to the conviction that the quest for a kinder cure is attainable so long as research supported by Bloodwise, through the generosity and commitment of so many people and partners, continues – which it will – given the overwhelming importance of this cause.

# How our journey began

Back in 1960, if a child was diagnosed with leukaemia, it invariably meant the end of their young lives.

The loss of a child is something no family should have to suffer, but thanks to the strength and endurance of one family that did, 8 out of 10 children diagnosed with acute lymphoblastic leukaemia today survive in the long term. We won't stop until they all do.

The Eastwood family lost their precious daughter, Susan, to leukaemia when she was just six-years-old. They channelled their grief in the only way they knew how – by fundraising to find a cure and save other families from similar heartache. By 1961, they had galvanised enough support across the UK to open the first leukaemia research unit in Great Ormond Street Hospital.

Bloodwise is the legacy of their endeavours. Today, we operate as the UK's specialist blood cancer research charity, and we still apply the same determination to finding a cure and supporting families in their most challenging of days.

For more information visit  
[bloodwise.org.uk](http://bloodwise.org.uk)





# Bloodwise

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