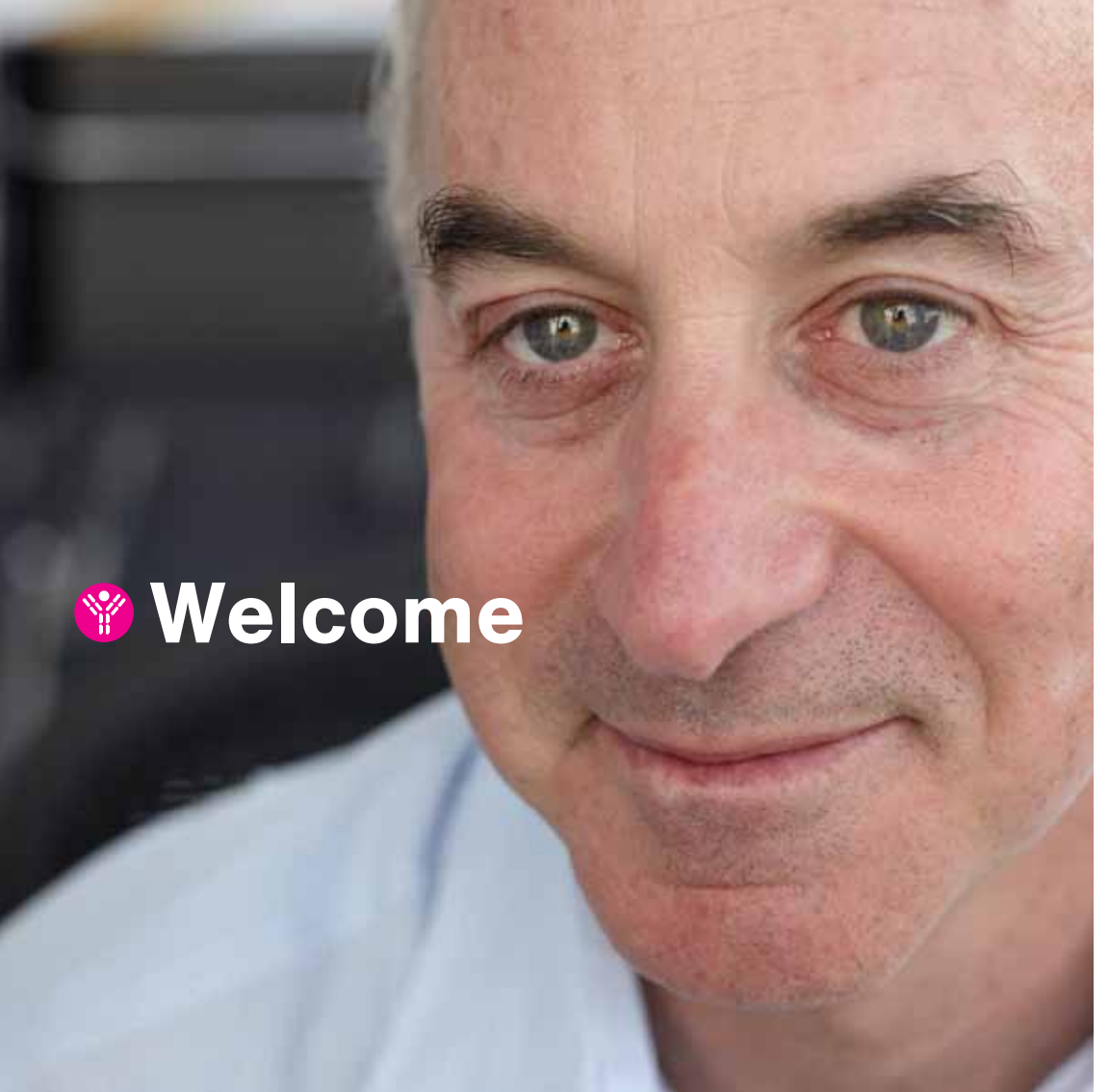
Great Ormond Street Hospital Charity

Breakthroughs in children's medicine

Immunology



Welcome

Welcome to our breakthroughs in children's medicine guide, focusing on immunology. This guide features a variety of diseases that come under immunology, including sever immuno deficiency, arthritis, DuGeorge syndrome and HIV. Great Ormond Street Hospital has always been at the forefront of immunology research and over the past 160 years we have come a long way in discovering how our body protects itself against disease and infection.

We have gone from lacking understanding of how diseases affect the body, to developing an understanding of how our body's immune system works and translating this information into effective new treatments to fight complex and rare diseases in children.

In the last 50 years, Great Ormond Street Hospital, together with its dedicated research partner, the UCL Institute of Child Health, has led the way, appointing the UK's first dedicated Professor of Paediatric Immunology and performing the UK's first bone marrow transplant in a child. Today our teams are leading global efforts to undertake cutting-edge gene therapy clinical trials in several disease areas.

Immunology is still a relatively new field of science and ongoing research is therefore vital to help us continue developing new treatments and cures that will benefit both children and adults worldwide.

I hope you enjoy reading about Great Ormond Street Hospital's history of pioneering immunology work and that you continue to support our vital progress.

Professor David Goldblatt,
Director of Research and Development,
Great Ormond Street Hospital

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Yesterday

Disease rife in 19th century London

London in the early 1840s was an infection-ridden city. Diseases such as smallpox, tuberculosis, cholera, scarlet fever and diphtheria were claiming the lives of 50,000 people a year.

The young were particularly at risk of death from infection. Of over 2,300 patients being treated in London hospitals in 1843, only 26 were under the age of ten.

At the time, medical care was simply not on offer to young children, and those under the age of 10 could only be admitted if they required surgery. For a time, Guy's Hospital was an exception, providing 15 cribs in a building over some stables. But when this building was pulled down in 1850, it was not replaced.

In the mid-19th century, people didn't know what caused fevers, or how infectious diseases spread. When it came to children, mothers were considered to be best-placed to provide their care. This, combined with a pervading fear of the spread of infection, meant that Dr Charles West, the founding physician of the Hospital for Sick Children at Great Ormond Street, faced a grim challenge.

Realising that these children needed special care and attention if they were to have any chance of survival, they opened the hospital's doors to patients in 1852. Children suffering from infectious diseases were sent to its top floor to isolate them from other patients.

This cramped fever ward quickly became the hospital's busiest. With only one nurse, and only the most basic treatments of milk, beef tea and wine on offer, many simply did not survive.

1852 The Hospital for Sick Children (now Great Ormond Street Hospital) opened with 10 beds.

This engraving of the hospital's early wards shows its founder Dr Charles West among nurses, patients and families in the original town house situated on Great Ormond Street.

The hospital's electrical department attempted a number of approaches that today might be considered unconventional. 'Sun-ray' treatment was offered to children with tuberculosis, not treatable with drugs until the 1940s.

Infection ever present

The continuing lack of understanding of how diseases affected the body, or how they were transmitted, meant that little progress was made in treating infection in the hospital's first 50 years.

An infectious diseases block was built in 1878 to try and control cases of fever. However, this did little to prevent its spread. Outbreaks of diseases such as diphtheria were not uncommon. One such outbreak in 1880 was thought to arise from the demolition of nearby buildings.

Emergency measures to close all windows, ventilators and openings did not prevent wards from regularly being shut down as a result of the number of infected patients. Having initially allowed families and wealthy patrons onto the wards, visiting hours were restricted to one hour on a Sunday – a strict policy which remained in force until the 1950s.

Despite this, by studying patients with similar symptoms admitted to the hospital, pioneers like Dr Walter Butler Cheadle began to gain vital insights into the nature of disease.

An example was Sydenham's chorea, which is a complication of childhood infection with Group A streptococcal bacteria. Sydenham's chorea caused uncontrollable jerking and joint pain. By carefully observing the symptoms of different groups of patients, Cheadle was able to describe precisely how the disease affected different parts of the body. A cure would only come with the discovery of penicillin decades later, but Cheadle's findings would be crucial to its future diagnosis and treatment.

1880/90s Multiple outbreaks of diphtheria regularly cause Hospital to shut down.

Change in the air

Patients had been encouraged to take in ‘fresh’ air – which at the time was more than likely thick with pollution – since the hospital’s earliest years. The hospital even rented garden space from the nearby Foundling Hospital so children could “take the airs”. When newer clinical buildings were built, all had balconies onto which children would be wheeled out, regardless of the weather.

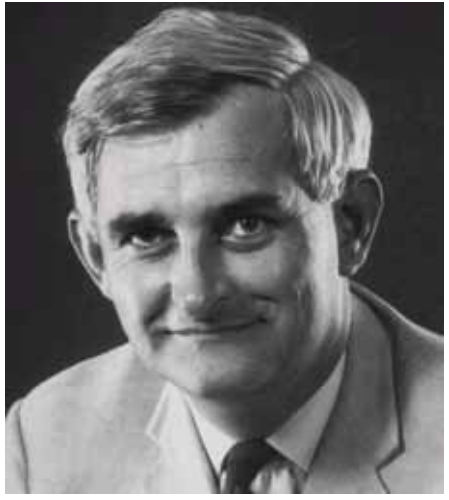
Actual treatments for infection remained rudimentary. Nevertheless, the hospital kept at the forefront of what emerging technology was on offer at the time. In 1934, the hospital purchased the UK’s first iron lung, officially named the Drinker Respirator. This frightening contraption was used to treat patients with severe muscle paralysis resulting from infection with polio. The machine helped to expand children’s lungs, allowing them to breathe and providing an alternative to frequent surgery.

In 1938, a new 10-floor clinical block (now the Southwood Building) was built, replacing long open Victorian wards with multiple smaller units. As well as being more patient-friendly, these modernised facilities dramatically reduced the number of fatal infections. In the case of children treated for pyloric stenosis – a dangerous narrowing of the stomach requiring surgery to allow its contents to pass into the small intestine – procedure-related fatalities plummeted from one in five, to fewer than one in a hundred children.

These first signs of improvement in treating infection represented the first steps toward what would be remarkable advances in our understanding of how the body fights disease, including the discovery and manufacture of antibiotics in the 1940s.

A child in an early iron lung, being treated for polio. The device applied suction to the patient’s chest, overcoming their paralysis to expand the lungs and help them breathe.

The UK's first professor of paediatric immunology



Above: John Soothill, the UK's first Professor of Paediatric Immunology

Until now, science had been making steady progress in describing the agents of disease – bacteria, viruses and other foreign 'germs' but very little was known about how the body defended itself. This in turn limited the types of treatment that could be offered to children whose immune systems were either compromised, or under attack from disease-causing agents that did not respond to antibiotics such as penicillin.

Research was desperately needed to understand the biology that underpinned our immunity to disease. So the hospital appointed John Soothill as the UK's first dedicated paediatric professor in the important but relatively uncharted new area of immunology.

Professor Soothill realised that despite Great Ormond Street Hospital's near exclusive focus on very sick children, more common diseases should not be ignored. His work explored the causes of asthma, eczema, rubella and allergies. He also studied children who seemed particularly susceptible to severe and recurrent infections.

He faced an immense task: to unravel the incredibly complex sequence of interactions that take place between different biological molecules, triggering a disease-fighting immune response. This painstaking work – carried out from a laboratory initially consisting of himself and one technician – would require years of carefully extracting proteins, purifying them, and performing tests to try and reveal their function.

Emeritus Professor Malcolm (Mac) Turner, a colleague of Professor Soothill at the time, reflects on his experience of working with him:

"It was incredibly exciting. Though scientists had known about antibodies since the turn of the century, no one had much of a clue how they worked, or how many types of them there were. John was a tremendous enthusiast, but also determined to take his time and really understand how our growing knowledge of the immune system could help patients with both rare diseases and more common ones."

Professor Soothill's early insights would pave the way for quite revolutionary treatments in the years to follow.

Above: Tony Medlen, a researcher working in the immunology laboratories in the 1970s to explore the disease-fighting properties of certain biological molecules

A growing arsenal

Having helped colleagues Alastair Dudgeon and Bill Marshall to kick-start the UK's first national vaccination programme for rubella – a disease all but eradicated today – the work of Professor Soothill and his growing immunology team was set for a number of vital breakthroughs.

Of particular concern to Professor Soothill were groups of children who had little or no resistance to germs: even a common cold could prove fatal. These so-called "bubble boy" diseases were named due to the total isolation that young children had to undergo, to keep them free from infection.

Professor Soothill was the first to name these devastating conditions severe combined immunodeficiency syndromes (SCID): diseases arising from the body failing to produce the white blood cells required to recognise and attack germs.

During the 1970s, it was Roland Levinsky (pictured right) – later to take over from Professor Soothill – who led efforts to explore how these vital cells might be isolated from bone marrow, the spongy tissue inside bones that gives rise to all of the body's blood cells.

In a landmark procedure in 1979, Professor Levinsky attempted the UK's first operation to transplant cells from a healthy donor into the bone marrow of a patient with SCID. Though not without serious complications, the procedure was ultimately a success, curing young Andrew Williams of his disease.

It would mark the beginning of a new era of medicine, using the living agents of the body's own immune system to combat what had previously been fatal conditions.

1970 UK-wide immunisation of girls and childbearing adult females rolled out for rubella.

1980 Roland Levinsky cures fatal immunodeficiency with UK's first paediatric bone marrow transplant.

Andrew's pioneering bone marrow transplant

At four months old in 1980, Andrew fell severely ill with gastroenteritis, and was admitted to hospital so that doctors could keep a close eye on him.

However, when doctors carried out a blood count, they discovered that Andrew had no disease-fighting white blood cells – he had no immune system whatsoever. Andrew was immediately referred to Great Ormond Street Hospital, where Professor Roland Levinsky diagnosed him with a form of severe combined immunodeficiency syndrome. He informed the family that Andrew's only chance of survival was to have a bone marrow transplant – a highly experimental therapy that had never previously been trialled in a child in the UK.

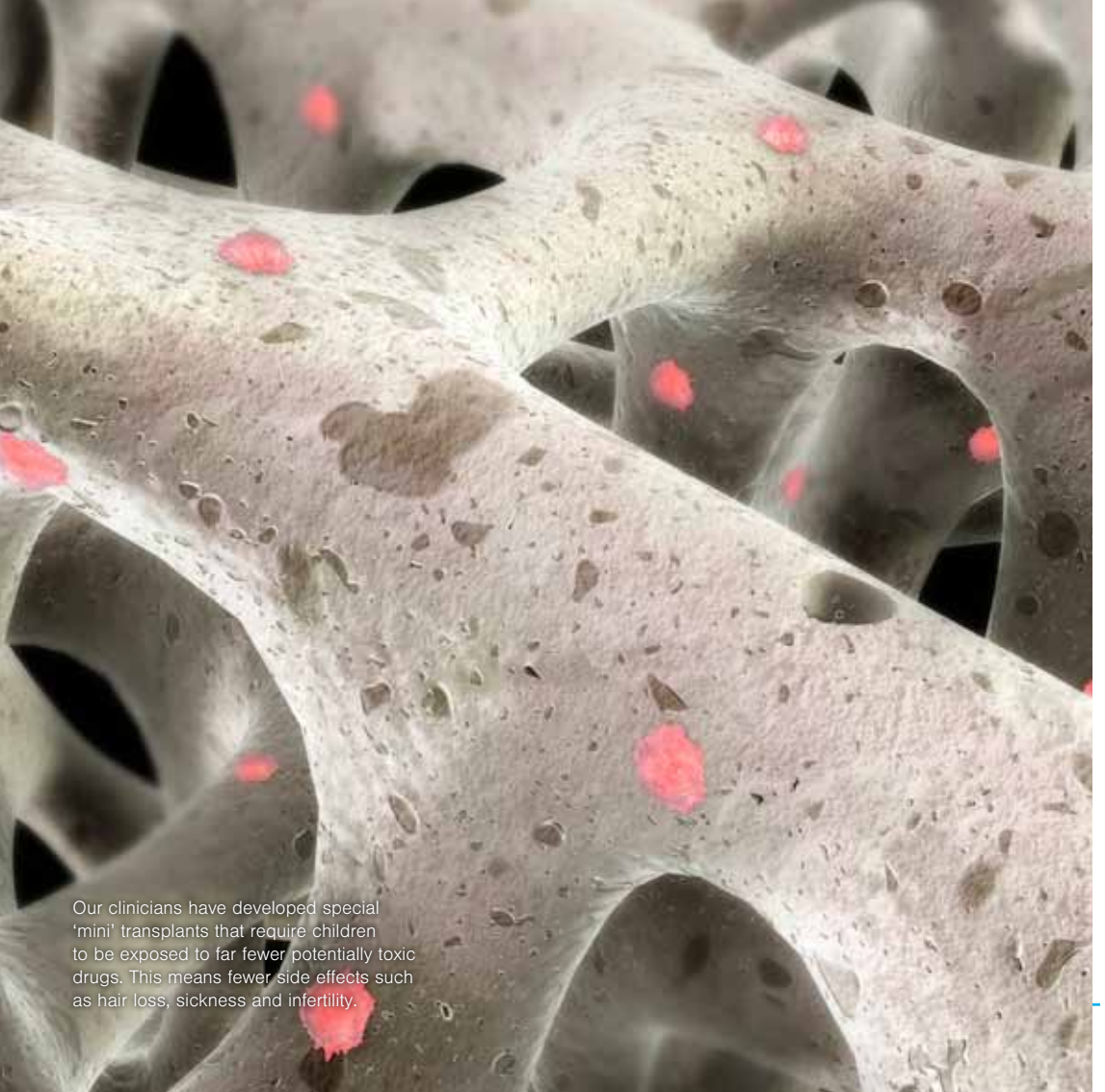
Andrew's elder brother, who was three years old at the time, was identified as having a tissue match. The transplant was carried out later that month and within a matter of days, Andrew suffered a serious setback due to the onset of graft-versus-host disease, where the donor cells realise that they are in an 'alien' body and start to attack it.

Finally, thanks to the use of steroids, the donor bone marrow cells began to settle and Andrew was able to go home in January of the following year. Andrew went on to have a normal and healthy childhood, and is now 33 years old.

He says: "I was too young to remember my experience as a patient and the bone marrow transplant procedure, but I realise how lucky I am to be here. I really do believe that fate took me into Professor Levinsky's capable hands all those years ago and I'll never forget that I owe him my life."

Andrew Williams, who was the UK's first child to undergo a life-saving bone marrow transplant.

Today



Our clinicians have developed special ‘mini’ transplants that require children to be exposed to far fewer potentially toxic drugs. This means fewer side effects such as hair loss, sickness and infertility.

Learning the language of immunity

Prior to the UK’s first paediatric bone marrow transplant, Soothill led an era of research that helped to define the tangled web of molecules that interact to provide immunity to disease. Having taken over from him in 1985, Professor Levinsky oversaw a period of profound change for the treatment of patients.

Ever the innovator, he was able to generate tailor-made antibodies, a form of biological lock into which specific molecules fit like a key. Where initially Professor Soothill had helped to discover the role of antibodies in triggering the body’s immune response against disease, Professor Levinsky used these newly engineered antibodies to isolate and extract the stem cells that grow into disease-fighting white blood cells.

We can now manipulate these stem cells to control their ‘attack’ response when transplanted into patients. This vital work means that today, Great Ormond Street Hospital is one of the world’s leading centres for carrying out bone marrow transplants.

In parallel, the last three decades have seen a revolution in our understanding of the human genetic code. Professor Levinsky’s team was one of the first to identify the specific mistake in patients’ DNA that caused X-agammaglobulinemia – a condition which stops the body from producing antibodies.

At the time, it took over five years to pinpoint which faulty region of the DNA code caused the disease. Nevertheless the teams went on to identify the genetic basis of many of the most challenging immune diseases. By providing the missing link to understand the fundamental biology of these often rare conditions, this knowledge paved the way for an accelerated programme of developing treatments now available to patients who urgently need them.

1992 Our researchers help identify the first genetic cause of life-threatening immune diseases.

Helping children whose immune systems turn on themselves

Originally known as 'rheumatic' diseases, these often devastating conditions range from juvenile onset arthritis, where immune cells attack the bones and tissues of the joints, to severe forms of inflammatory diseases, forcing children's bodies into a near-permanent state of fever.

First formally described by Great Ormond Street Hospital's own Sir George Frederic Still in 1896, this series of diseases have long been a focus for ground-breaking research efforts over the years.

Until recently, few treatment options existed for these children, who could face crippling deformities of their joints, or constant flu-like symptoms such as aching and abdominal pains. But research at the hospital throughout the 1980s began to identify a class of immune cell 'messenger' molecules – called cytokines – as a potential target for these diseases.

Today our teams are leading global efforts to undertake clinical trials of new types of therapies, which act to block the incorrect cytokine trigger that causes the disease. When successful, the change is remarkable: the over-active immune cells are forced into a state of quiescence, with children's lives rescued as a result.

Modern genetic sequencing techniques are also allowing our clinicians to understand why some of these children do not respond to treatment. It marks an exciting first step towards a more personalised form of medication, where therapies are based on a child's unique genetic makeup – a future Sir Frederic would have had little chance of imagining.

 1998 Bone marrow transplant therapy successfully trialled as a cure for drug-resistant arthritis.

Ffion was born with a severe combined immunodeficiency (SCID) called Omenn Syndrome and is being treated at Great Ormond Street Hospital.

Matilda’s story

A few months after Debra stopped breastfeeding her baby, Matilda showed signs of fever and pain. She was taken to her local hospital, where doctors suspected meningitis.

At 15 months, Matilda had severe complications and was eventually transferred to Great Ormond Street Hospital (GOSH). Following a series of tests, Matilda was diagnosed with chronic infantile neurological cutaneous and articular syndrome (CINCA), a rare condition that affects the joints, skin and development of organs such as the brain, eyes and ears.

After being put on a range of steroids, Matilda’s mum, Debra, says: “The difference was remarkable. Within a few weeks her symptoms had died down and after three months she no longer needed oxygen and was drinking and eating like a normal toddler.”

Matilda returned home and started attending her local play group and school. Although she was unable to walk properly, she enjoyed life as best she could.

But in 2011, Matilda was readmitted to GOSH with heart failure and pneumonia. She went into cardiac arrest, but was saved thanks to the rapid response of the clinical staff.

Matilda is now in a wheelchair and attends a special school. A cheeky, vibrant character, Matilda has learnt to live with the pain, which sometimes flares up, but at other times is manageable. “She struggles sometimes, but she does her best,” says mum Debra.

While there is currently no cure for CINCA, it’s children like Matilda that keep our doctors and researchers striving to find new and better treatments for these rare conditions.

Gene therapy: your DNA becomes its own medicine

During his time as Dean of the UCL Institute of Child Health (ICH), Professor Levinsky delivered a vision that saw research integrated into the heart of the hospital. He recruited new and talented young scientists, hugely increased funding income, and oversaw daring new programmes of experimental medicine focused on improving patients' lives.

Arguably none was more daring than his bold idea that children born with diseases arising from damaged or absent genes might be cured by introducing healthy working copies of those genes into their bodies.

Levinsky and his team had developed techniques to isolate faulty bone marrow stem cells, and these became a perfect target for therapies designed to treat cases of severe immune diseases such as severe combined immunodeficiency syndromes. However a further challenge lay ahead. They would have to manipulate viruses as living micro-robots, to safely deliver vital healthy copies of genetic material into the inner DNA-filled nucleus of the stem cells – and then re-introduce these cells back into a patient's bone marrow to grow.

Only after more than a decade of rigorous safety testing are these remarkable gene therapies now in a position to be considered a viable cure – with the lives of more than 17 children with immune diseases testament to the dedication of the hospital and ICH's clinical research teams.

One of our clinical researchers working under the incredibly clean conditions required to prevent contamination of live gene and cell therapy products. We are one of only a few hospitals in the world to offer these remarkable new treatments.

2000 World's first gene therapy trials begin for children with severe combined immunodeficiency syndromes.

2011 Gene therapy cures fourteen children with previously fatal forms of SCID.

Child-friendly facilities to stop infection

In keeping with its long-standing history of helping children often too sick to be seen elsewhere, today Great Ormond Street Hospital houses one of four specialist paediatric infectious disease units in the UK. Our specialist teams look after children referred from other hospitals to be treated for life-threatening infections like malaria, meningitis and tuberculosis.

Modern facilities are crucial to preventing the spread of some of these diseases. Thanks to the generosity of our supporters, we recently opened the doors of the Morgan Stanley Clinical Building, the first of two new buildings that together will form the Mittal Children's Medical Centre.

As well as significantly increasing the number of patients we can treat, several rooms have special air handling units that can isolate infection. A patient with any contagious disease can have airflow contained within their room during their treatment, while the rest of the ward continues to operate normally, ensuring that other patients receive the care they need.

With the latest equipment, we can also now identify disease-causing micro-organisms using gene screening technology. Our rapid diagnostic facility can find the cause of an infection within hours – crucial if our clinicians are to take action to treat and stop the spread of disease.

One of the isolation rooms in the Morgan Stanley Clinical Building. Special airflow units can pump air in or out of the room to contain or keep out infection, protecting patients from life-threatening exposure to airborne diseases.

Meet the team

We're in the midst of a remarkable revolution in our understanding of genes and how they work. When I started here in the early 1990s, the science of gene therapy was largely confined to the research laboratory. Gradually the techniques have improved, so much so that we can now contemplate using DNA as a medicine.

To do this we've had to put in place new state-of-the-art buildings and equipment that enable us to translate our discoveries – such as how the immune system works – into effective new treatments to fight complex and rare diseases. All of this work involves scientists, doctors, nurses and the patients and families themselves.

I'm proud to say that today Great Ormond Street Hospital (GOSH) is at the forefront of gene therapy worldwide, bringing new hope to future generations of patients who until recently have never had the chance of a life-long cure.

Adrian Thrasher, Lecturer Practitioner in Immunology

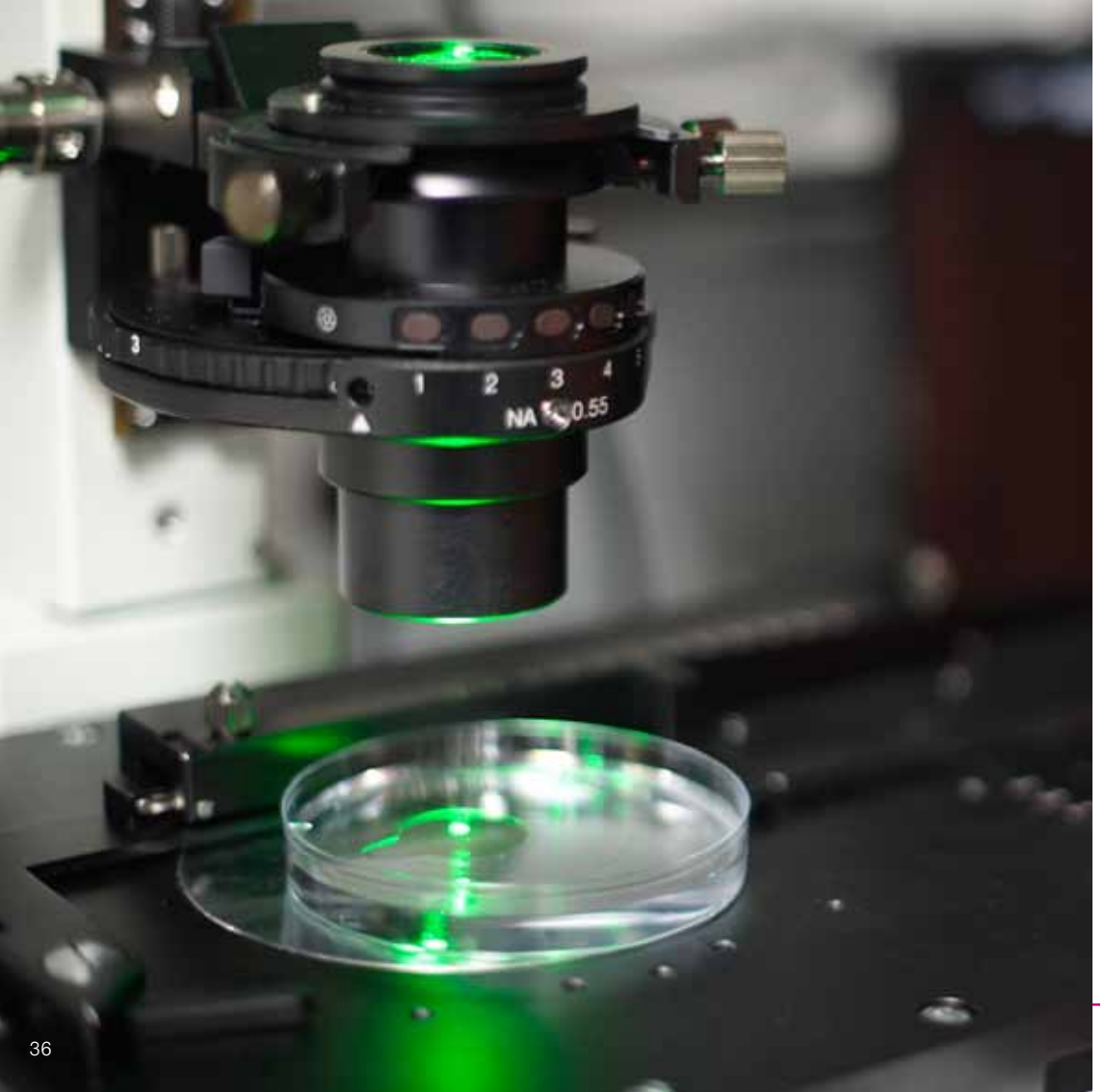
Having arthritis affects every part of a young person's life. It can prevent them from keeping up with their friends or attending school or college full-time. Our new Arthritis Research UK Centre for Adolescent Rheumatology will help us to meet the needs of teenagers growing up with arthritis. By better understanding why and how arthritis is different in adolescence, and what happens as they become adults, we hope to dramatically improve treatment and care for young people living with this painful disease. Rheumatology is an exciting field of research. New drugs that stop the inflammation of arthritis are becoming available. Our research will look at ways to predict which medicine works best for each young person, to allow them to resume a full, normal life. The centre's talented researchers will take our work forward, with regular input from patients, families and clinical staff to guide our research. It's a privilege to lead such a dedicated, world-class facility.

Lucy Wedderburn, Honorary Consultant in Rheumatology

During the past few decades there's been a huge increase in both our understanding and awareness of primary immunodeficiency disorders (PIDs). Improvements in the diagnostic investigations and available treatments have brought improvements in long-term outcomes for children affected by these rare conditions. The Immunology department at GOSH is one of the largest specialised units providing services to children with PIDs. The team provides care from diagnosis – which in some cases is before birth – through treatment by stem cell transplantation (in collaboration with the bone marrow transplant team) or gene therapy for some of the very severe disorders, while other children require lifelong supportive treatment.

Alison Jones, Consultant Immunologist


Tomorrow



A brighter future

Seeing so many children with rare and often life-threatening diseases has always prompted our staff to pioneer new and better treatments, to offer them the chance of a healthier life.

This drive to innovate is now delivering a programme of research to transform the medicine of tomorrow.

Our world-leading gene therapy has opened up a new gateway to medicines that deliver a life-long cure, with minimal side effects. For children born with a damaged or absent immune system, this means they can begin to look forward to a life free from the fear of a lethal infection with every human contact. In some cases it has the potential to save the NHS millions of pounds, replacing costly and painful regular injections of missing enzymes with a single treatment.

Lying behind these achievements are our dedicated clinical and research teams, working together to identify how to help the hundreds of patients treated by our immunology teams each year. They are applying the very latest advances in how the cells and molecules of the body's immune system work, to re-engineer our natural response against infection. Not only this, but they are beginning to teach the body's immune system new tricks – work that may provide a vital line of therapy for previously untreatable conditions.

Much of this work is being sustained thanks to the generous supporters of Great Ormond Street Hospital Children's Charity. Our patients are a living testament to what this support has achieved so far – but we are even more excited about what the future could hold.

A life-saving transplant to re-establish children's immune cell training ground

One of the key organs responsible for producing the body's immune cells is the thymus. It acts as a factory for an important group of blood cells known as T cells, which fight infection and regulate other parts of the immune system. The organ also acts as a T cell school, educating them to fight invading germs yet not attack the body's own 'self' cells.

In very rare cases of a disease called DiGeorge syndrome, children are born without any functioning thymus. Similarly to children with severe combined immunodeficiencies, this results in children having a profound risk of infection, due to the absent T cells.

Dr Graham Davies, Consultant Immunologist at Great Ormond Street Hospital, has led research to offer these children a lifeline. He has developed a technique to transplant cells from donated thymus tissue into patients with DiGeorge syndrome.

For patients and families receiving the new therapy, its impact is significant – until now, they would have had to travel to the United States to receive such a treatment. Already saving patients' lives, Dr Davies is excited about its potential:

"Research to develop this complex therapy continues to reveal new insights into how our immune system works. It is another example of how we're constantly refining our knowledge of how the body fights disease. In time, I hope thymus transplantation could be used to improve the outcome for a much broader range of severe clinical conditions affecting both children and adults."

Rachel Kiefte reflects on her family's experience following her son Charlie's thymus transplant at Great Ormond Street Hospital:

> *"We finally feel Charlie will have the chance for a normal life, where he is able to mix with others without us worrying constantly about him picking up infections. We are so grateful to Graham and his team at Great Ormond Street Hospital. We think he has given Charlie the chance to live a proper life."*

Tailor-made antibodies and a new therapy for HIV

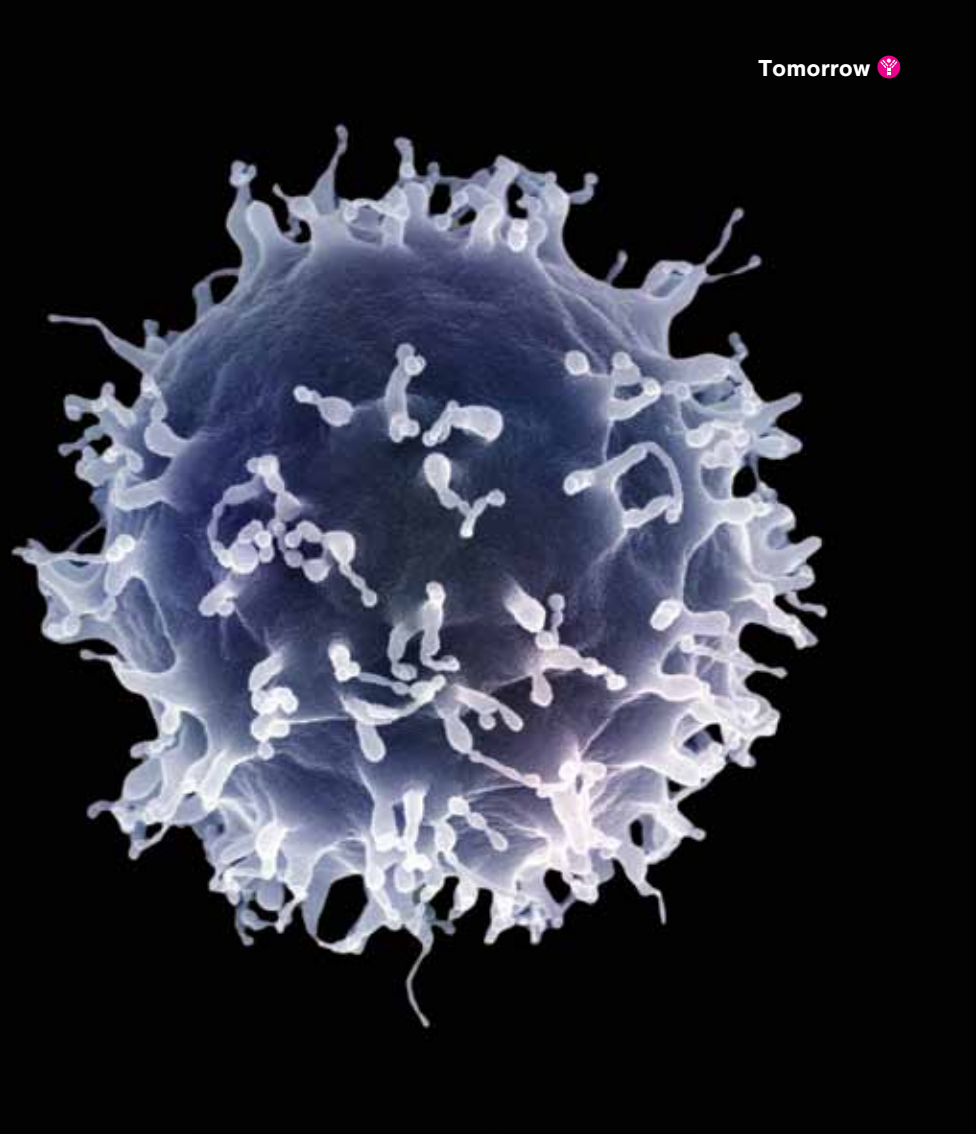
Saving the lives of over 70 patients a year, our gene and cellular therapy programme is a success story of which our early pioneers would have been rightly proud. Now, as part of an exciting expansion of our clinical research facilities, leading researchers such as Dr Waseem Qasim at the UCL Institute of Child Health's Molecular Immunology Unit are taking this work to the next level.

His team have developed a method of delivering gene therapy that turns HIV against itself. It relies on the virus' unparalleled ability to infect human T cells with its own DNA. Ordinarily, this would cause the death of these vital cells which, if left unchecked, results in the onset of AIDS.

Right: A human T cell – one of the vital disease-fighting cells of the immune system, which our researchers are now re-engineering to treat previously incurable conditions.

Remarkably, the team are instead using a disabled version of the HIV virus itself to transfer a protective gene into the body's T cells. This gene carries the instructions to produce a special protein, engineered to mirror the function of one found in certain rhesus monkeys, naturally immune to HIV.

The technique stands to offer a new line of therapy for children who have been on antiretroviral drugs for their entire life – potentially, a vaccine for HIV. It forms just one strand of a pioneering programme of research to artificially engineer new disease-fighting antibodies and cells, which could revolutionise the treatment of not only infectious diseases, but rare diseases of the gut, skin and even the severest forms of cancer.



Thank you

We have come a long way in the past 160 years. Our dedicated and passionate staff have pioneered many new, and better ways of treating some of the sickest children. But we are yet to cure all of the patients we see.

Throughout our history, it has been the continued and generous support of our donors who have helped to fund the research that provides new breakthroughs. With their ongoing generosity we seek to give hope to every child that needs our specialist help.

Right: Jazmyn regularly attends Great Ormond Street Hospital for treatment for her arthritis.

Find out more

Our website has more information about the specialists, patients and treatments you've read about in this guide, as well as the pioneering research the hospital carries out.If you'd like to find out more, attend one of our special research breakthrough seminars or you have your own stories that you'd like to share with us, please visit gosh.org/breakthroughs

To continue the legacy of breakthroughs at Great Ormond Street Hospital, we need to raise £50 million every year. This helps to rebuild and refurbish the hospital, buy vital equipment and fund pioneering research. As well as the developments in this guide, amazing things happen at Great Ormond Street Hospital every day.