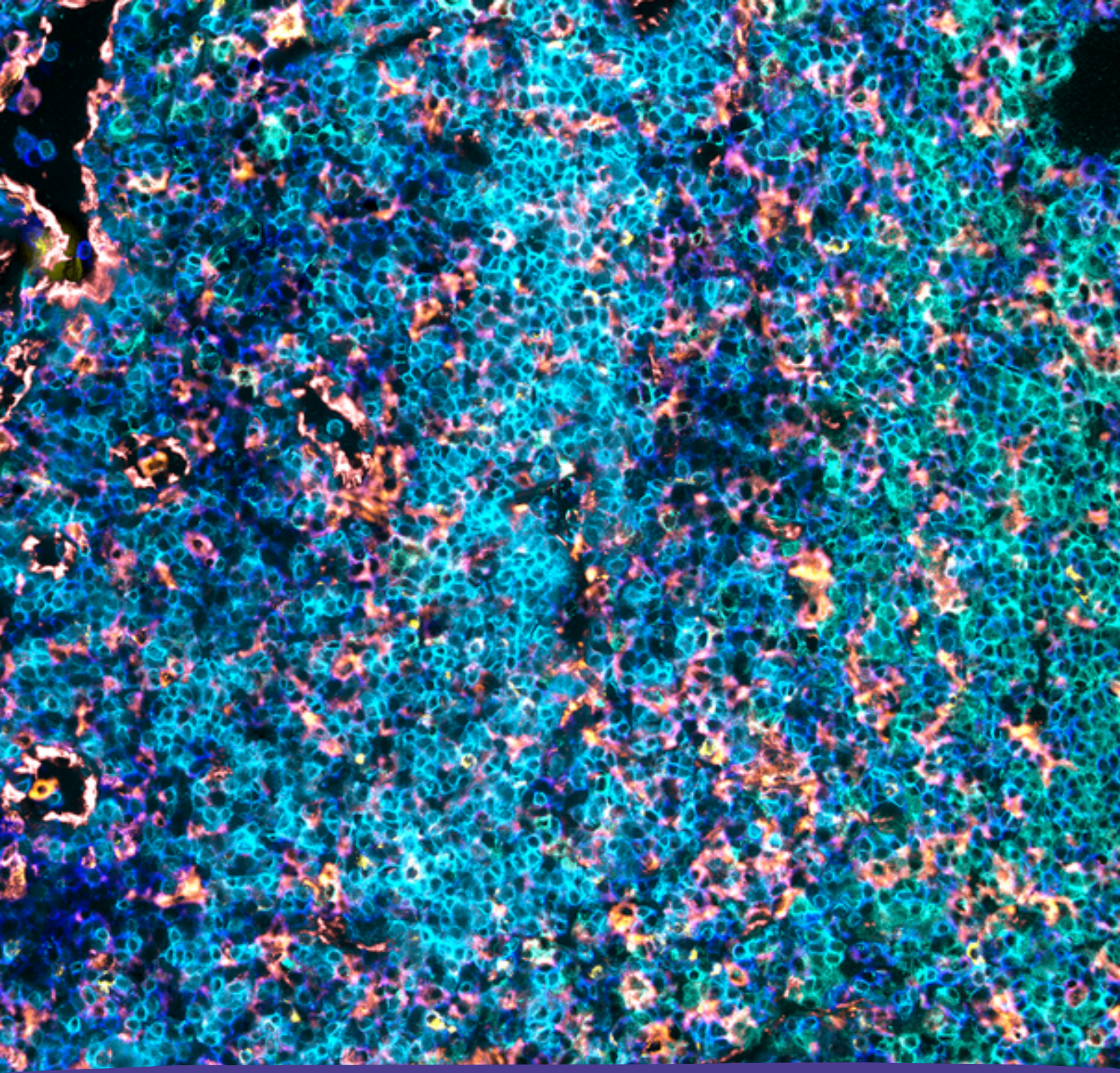

DMG CAR T-Cell Therapy Clinical Trial 6 Month Report Prepared for

Lyla Nsouli Foundation for Children's Brain Cancer Research

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GREAT ORMOND STREET HOSPITAL CHARITY

INTRODUCTION

Cancer happens when something goes wrong with the genetic code (DNA) inside cells, causing them to multiply out of control. It can happen to any type of cell in the body, from skin cells to heart cells. Cells that divide frequently are the most likely to become cancerous, because the more they divide, the more chances there are of errors creeping into DNA.

Children at Great Ormond Street Hospital (GOSH) have some of the most complex, rare and difficult-to-treat types of cancer. These include blood cancers like leukaemia, and tumours growing in delicate areas of the body such as the brain and spinal cord. The most life-threatening are those that come back after treatment (relapse), or that do not respond to treatment at all. Treatment usually consists of a multipronged attack, sometimes involving radiation therapy (radiotherapy), drugs infused into the body (chemotherapy) and surgery to remove cancerous tissue. As scientific understanding progresses, treatments are changing, becoming more tailored to the specific cancer type and even the individual child it affects.

We need to improve cancer outcomes – allowing children to lead better, longer lives with and after cancer.

Great Ormond Street Hospital entrance

Cover image: This image won GOSH's 2022 research imagery competition. The sea of blues and pinks captures the different immune cells flowing through our tissues at any one moment. Each cell has a specific role to play within the tissue. For example, the cells coloured in light blue that form what looks like a river running through the centre of the image are T-cells. These are part of the adaptive immune system and help fight infection. Immune cells, particularly T-cells, play a vital role in fighting cancer. The team generated this image using a technique called chip cytometry, which they hope will help to improve understanding of how T-cells interact with other cells within a tumour.

MOVING FROM STRENGTH TO STRENGTH

As the largest paediatric research and training centre in the UK, and one of only a handful of internationally recognised centres of excellence in the field of child health, GOSH continues to play a central role in improving the odds for children with the hardest-to-treat cancers.

The hospital is a world leader in gene and cellular therapies for children – a new generation of treatments tailored to each individual child that offer hope for lifelong cures. The Genomics Laboratory Hub, hosted at GOSH, and the opening of the new Zayed Centre for Research into Rare Disease in Children (ZCR) mean we have the infrastructure to provide genetic diagnoses and to develop novel pioneering therapies.

Within ZCR there is a major new good manufacturing practice (GMP) suite including 7 specialist clean rooms for the production of clinical grade gene and cell therapies and a simulation suite for education and training. The facility is the largest single academic manufacturing unit for gene and cell therapies in the UK and one of the largest in the world. Cell and gene therapy products are manufactured specifically for each patient and often have a shelf-life of only a few hours, therefore manufacture on-site at GOSH can be crucial in delivering these treatments to patients. The Centre brings together pioneering research and clinical care under one roof to help drive forward new treatments and cures for children with rare diseases.

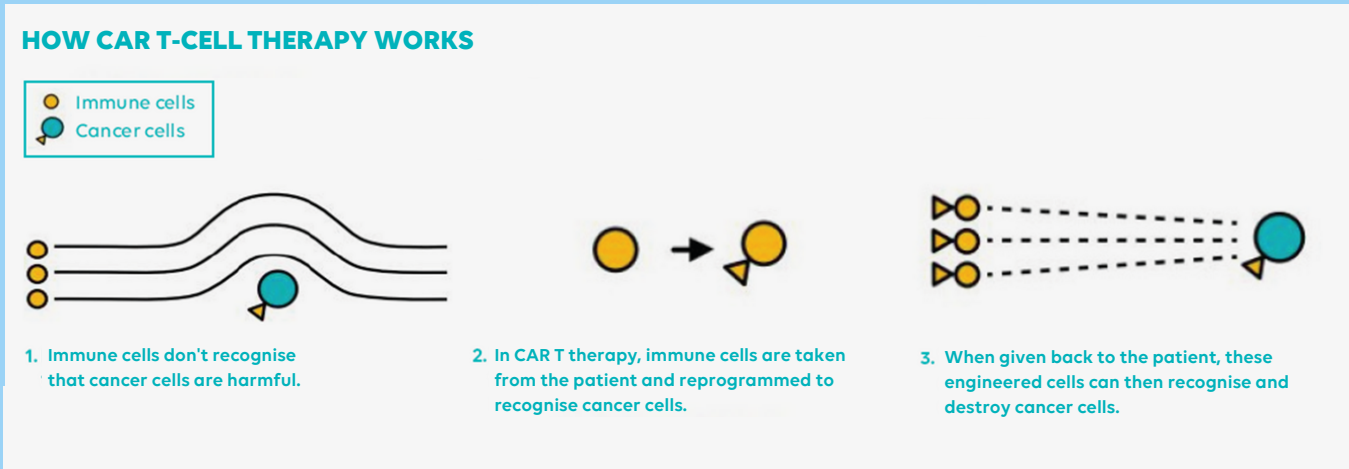
Gene and cell therapy facility

While broad-brush chemotherapeutic compounds can effectively destroy cancer cells by preferentially effecting rapidly dividing cells, the damage to healthy cells is unavoidable. And although radiotherapy strategies often provide a more targeted method of cancer treatment, they too can cause damage to the surrounding healthy tissues. Although the body's immune system can protect against foreign particles and even combat some cancerous cells, cancer cells often go unseen and grow unchecked.

In the last decade, researchers have discovered a way to overcome cancer's evasive properties and a new wave of targeted treatments have arrived - immunotherapy. These therapies are developed to either activate or suppress certain aspects of the immune system to treat auto-immune disease or cancers. The hope is that with these therapies, the damage to healthy tissue is minimised, vastly reducing the risk of side effects. A type of immune cell called T-cells have receptors on their surface that can bind to specific proteins on the surface of cancerous cells and once they bind, the cancer cells can be destroyed. However, the ability for T-cells to identify cancer cells is limited. One emerging therapy to overcome this issue, is CAR T therapy.

CAR T-CELL THERAPY AT GOSH

CAR T-cell therapy involves reprogramming the body's own T-cells to target cancer cells. The process involves removing some of the patient's blood, isolating the T-cells and genetically modifying in the lab to contain a molecule called a Chimeric Antigen Receptor (CAR), which is developed to selectively bind onto molecules (or targets) on the surface of a given cancer type.



GOSH researchers are leading the way in Europe in applying this incredible technology to acute lymphoblastic leukaemia (ALL) that has relapsed after treatment. In this instance, T-cells were genetically modified to contain a new type of CAR molecule (called CAT-19) to target the surface marker CD19 on cancer cells. The modified CAR T-cells were used to treat 14 patients with relapsed ALL at GOSH, Manchester Children's Hospital and University College Hospital, London. Published in Nature Medicine, the results show that after receiving the CAR T treatment, 12 out of 14 patients with otherwise incurable ALL cleared their disease after three months. Promisingly, high numbers of the CAT-19 CAR T-cells were still present in the blood after the cancer had been cleared, enabling the body to keep fighting against the leukaemia even years after treatment.

Following on from this, in 2018 an 11-year-old boy became the first NHS patient to receive the first licensed CAR T-cell therapy, Kymriah, for relapsed ALL and the child remains cancer free to this very day. Allowing hope of a life-long cure for previously incurable cancers.

CAR T-CELL THERAPY FOR DMG

At any age, cancer is life-changing diagnosis. And even though kinder, more effective treatments have been developed for many cancers, this is not the case for diffuse midline glioma (DMG), until recently known as diffuse intrinsic pontine glioma (DIPG).

Dr Karin Straathof, Associate Professor at the UCL Cancer Institute and Honorary Consultant at GOSH, and Professor Darren Hargrave, GOSH Charity Clinical Professor in Paediatric Neuro-Oncology and Honorary Consultant at GOSH, are looking to change that.

Professor Darren Hargrave

Dr Karin Straathof

The team have been working on a specific type of CAR T-cell which binds to surface marker GD2. GD2 is present at high levels on the surface of certain types of cancer cells such as neuroblastoma and DMG.

In 2016, Karin's team conducted the first phase 1 clinical trial for GD2 CAR T-cell therapy for neuroblastoma. This clinical trial was one of the first trials where CAR T-cells were used to treat a cancer that wasn't a blood cancer. The results showed clear evidence of immune activity of the CAR T-cells leading to a reduction in the tumour burden. One consideration when targeting GD2 is the potential to damage healthy cells as low level GD2 is also present on normal brain tissue and peripheral nerves. Importantly, no neurotoxicity has been seen in patients with neuroblastoma treated with GD2 CAR T-cells. There is a high level of GD2 on the surface of DMG compared to neuroblastoma, providing further plausibility of the success of this novel therapy for DMG.

More recently, work at Stanford University outlined that CAR T-cells using a different GD2-CAR design can successfully be produced from patients with DMG, and 3 out of 4 patients in the preliminary analysis were shown to have improvement in tumour size and symptoms, with no effect on healthy brain tissue. This represents the first significant advance in DMG in decades and encourages broad exploration of GD2 CAR T-cell therapy in this cancer.

Karin's team are investigating how to best give the CAR T-cells investigating two routes. The first will be intravenous (via a drip in the vein) and the second will be directly into the cerebral spinal fluid. Three dose ranges of CAR T therapy will be tested to determine the safe and most optimal dose of CAR T-cells for children with DMG.

MHRA APPROVAL

The Medical Health Research Association (MHRA) supports the conduct of trials with complex innovative designs and are an essential regulator of trials in the UK. Due to the nature of the GD2 CAR-T trial for DMG, it requires specialist staff to review the trial design and unfortunately the clinical trial team have experienced delays in the trial approval process. Once the team has received approval from the MHRA, they will begin the recruitment process. The initial comments received by the ethics committee were positive and the team expect to receive the appropriate approval in the coming weeks.

LOOKING FORWARD

Dr Straathof, Prof Hargrave and their team have worked with the UCL Clinical Trial Centre to prepare the clinical trial protocol and all supporting documentation. These documents were submitted to these regulatory bodies on 1st November 2022. The clinical study has been discussed with the ethics committee, and outcome of the MHRA review is awaited.

In the meantime, Karin and the team are ensuring every effort is made so that the trial can commence as quickly as possible once regulatory approval is in place. The study data bases has been developed which will allow the team at GOSH to collect the clinical trial date on one platform, allowing for seamless collation of study data. The supporting neuro-oncology consultants, fellows and research nurses are receiving specialist training on how to manage patients who are receiving CAR T therapy to ensure every child receives the best care possible while on the trial. Indeed, this will be the first trial in Europe where CAR T therapies will be investigated for brain tumours of any kind in children.

Dr Straathof and Professor Hargrave are working closely with colleagues at Stanford University in order to share learnings on how best to monitor children on the trial and handle any potential issues that may arise.

If GD2 CAR T-cells can be safely applied in DMG and evidence of clinical activity is seen, this will provide an important first step for further development of CAR T-cell therapy for DMG and other brain tumours where limited treatments are available.

THANK YOU

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