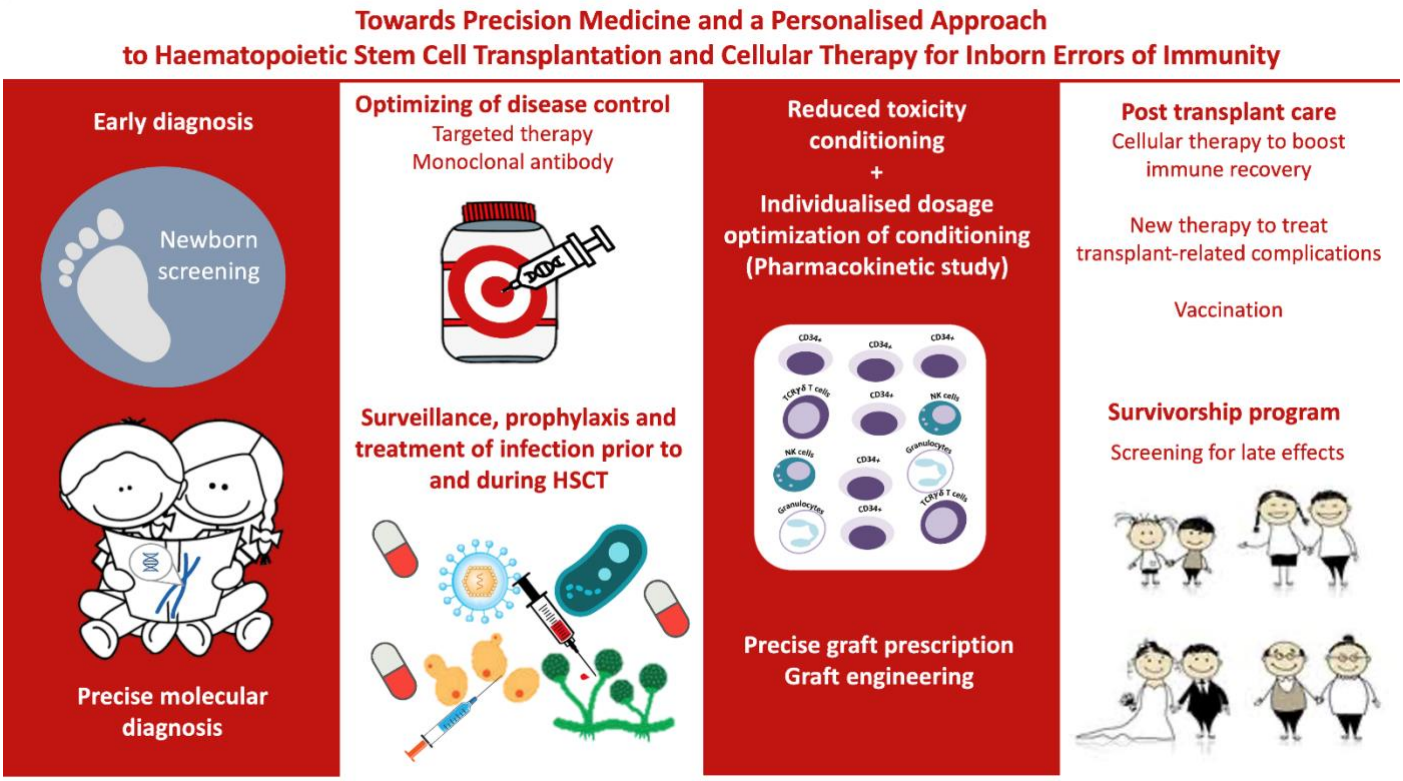

The Haplo+4kids clinical trial to improve haploidentical donor stem cell transplant for children and adolescents with immunodeficiency

The Paediatric Immunology and Transplant teams at the Great North Children's Hospital in Newcastle and Great Ormond Street Hospital in London are preparing to start recruitment to an exciting clinical trial called Haplo+4kids, funded by the UK Medical Research Council. The aim of this trial is to improve the transplant outcomes after a mismatched family or unrelated donor haematopoietic stem cell transplantation (HSCT; also known as a BMT) for children with inborn errors of immunity which is also known as primary immunodeficiencies. This trial is one of the important milestones to achieve precision medicine and a personalized approach to haematopoietic stem cell transplantation for children and adolescents with immunodeficiency.

The trial has been developed in collaboration with the Newcastle Clinical Trial Unit, Population Health Sciences Institute, Newcastle Cancer Centre Pharmacology Group and Leiden University Medical Centre. We are very grateful to Immunodeficiency UK and the Bubble Foundation for their active roles in patient and public involvement in designing this trial.

HSCT is the most widely available curative treatment for many children affected by severe combined immunodeficiency (SCID) and non-SCID inborn errors of immunity. Survival and outcome have significantly improved in recent years due to factors including earlier diagnosis, superior HLA (tissue) matching technology, an increased number of available donors, improved supportive care and treatment of infections and complications.

Improving transplant success for people without a suitably matched donor

Until very recently best results were obtained when an HLA-matched family or unrelated donor were used, but many patients do not have a suitably tissue-matched donor. An alternative is to use a mismatched related or unrelated donor and take out the donor's T cells prior to infusion. This is referred to as T cell depletion. Historically, the major challenges of using such mismatched donors were graft-versus-host disease (GvHD), transplant failure, and a high transplant-related mortality. Removing T-cells leaves the patient at risk of infection for at least 4 months post HSCT when the engrafted donor stem cells start to produce new T-lymphocytes.

Targeted removal of cell types that cause problems in HSCT

There are many different types of T-cells which play different roles in the immune system. Each type of T-cell is distinguishable by the markers it carries on its surface. Various methods are available to deplete certain T-cells based on these markers have been used over the years. A promising step forward has been the ability to selectively deplete the T cells that cause GVHD. These are known as CD3+ T-cell receptor αβ, or TCR αβ+ cells for short. Removing these cells decreases the risk of GVHD but leaves behind other 'good, helpful' T-cells, such as T-cell receptor-γδ+ cells, which help to fight infection (and leukaemia) and enhance engraftment.

Using a similar approach certain B-cell types can be removed to help improve outcomes for patients. For example, removing CD19+ B-cells decreases the risk of Epstein-Barr virus-driven post-transplant problems.

Using the combined approach of this specific B-cell and T-cell depletion strategy has been shown to provide rapid and sustained engraftment, faster immune recovery, and a low incidence of GvHD. In 2018 Newcastle and GOSH published a report of 25 patients who had this type of procedure with an overall survival of 84%. More recently Dr Su Han Lum and colleagues in Newcastle showed that survival was equivalent for children under 5 years of age whether they had a matched family/unrelated or a mismatched TCR αβ depleted donor transplant.

However, children over the age of 5 years, had a significantly lower overall survival following a mismatched TCRαβ depleted transplant compared to a matched family/unrelated donor transplant. Survival rates were lower due to viral infections and associated health complications indicating that an additional strategy was needed.

Giving back 'good' T-cells

The team at Newcastle have been working on a strategy to tackle these poor survival rates using an additional depletion step. This involves removing what are known as naïve GVHD-producing T-lymphocytes, amounting to about 10% of the donor cell harvest. This process leaves behind a pool of donor cells containing important memory T-lymphocytes (labelled CD45RO+) which can fight infection and enhance engraftment. Early results of giving memory T-cells back the day after the HSCT are extremely promising even in children over the age of 5 years with viral infection.

The Haplo+4kids project will assess different doses of the memory T-cells to find the best one and include detailed analysis of the drug concentrations, in the patient's blood, of the different treatments that are needed for 'conditioning' the patient's immune system prior to transplant. In addition, there will be careful monitoring of how the cells of the immune system recover after HSCT. Results will be compared between groups of patients – those who receive these extra cells to those who do not, and to outcomes of patients who have already undergone HSCT, including those people who received matched donor transplants.

The option of using mismatched donors who are often parents who are half-matched (haploidentical) to their child, means that every person who needs a transplant has a donor. This is revolutionising HSCT practice. The transplant can be arranged quickly and despite the laboratory costs of the cell depletions, may be more cost effective than using unrelated donors.

Header for photo: **The Haplo+4kids team**