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NIHR Blood and Transplant Research Unit in Precision Cellular Therapeutics

Precision cellular therapeutics are increasingly used to benefit patients.

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Professor Ronjon Chakraverty explains the work of his Blood and Transplant Research Unit, which seeks to accelerate the accessibility and clinical use of novel cellular therapies, with a particular focus on the patients' perspectives of these new technologies.

Our National Institute for Health and Care Research (NIHR) Blood and Transplant Research Unit (BTRU) in Precision Cellular Therapeutics is based at the University of Oxford and University of Birmingham and has been running now for 4 years. The programme supports 7 research groups, including 11 early career researchers, and is strongly aided by a committed patient group who bring expertise through their lived experience. Our research aligns to the broader NHS Blood and Transplant (NHSBT) Strategy in relation to supporting both innovation and the development and scaling of new cell therapies that can be delivered in the NHS.

The overall aims of our BTRU are twofold: first, we are seeking to accelerate the translation of novel advanced cell therapies into the clinic, as well as ensuring their wide accessibility across the UK population; second, we want to understand the impact of these new technologies from the perspective of patients. These aims are being addressed through 3 work packages, which are explained below.

Theme 1: Precision cell therapies for graft-versus-leukaemia

It has long been understood that allogeneic haematopoietic stem cell grafts work through their powerful induction of the graft-versus-leukaemia (GvL) effect, which is essentially a process of immune rejection of residual leukaemia cells by infused donor T cells. However, GvL can be a blunt process, and a broader immune attack upon patient tissues can lead to graft-versus-host disease (GvHD).

We are trying to improve the precision of GvL by identifying T-cell receptors (TCRs) that recognise leukaemia cells but do not react to other cell types outside the bone marrow. We have screened blood samples from transplant patients to pull out T cells with leukaemia-specific TCR, by identifying potential targets that are unique to cancer cells. In a gene therapy approach, isolated anti-leukaemia TCRs could be inserted into T cells and then infused back into patients.

We are also asking what kind of T cells would represent the best 'platform' for TCR gene therapy. To answer this question, we are looking at the results of our recent clinical trials, in which we infused specific T cell subsets. We are also using a combination of unbiased proteomics and functional assays to identify sub-populations of T cells from healthy donors with better therapeutic potential. Another approach we are testing to improve T-cell performance is through new gene editing techniques. Our ultimate objective is to pair the best candidate TCR with the best T-cell platform and use this as the basis for new T-cell gene therapies.

Theme 2: Graft manipulation and gene editing

A major issue following chemotherapy is the risk of severe infection secondary to neutropenia, especially for blood cancers and patients undergoing haematopoietic stem cell transplantation. There is little evidence to support the use of neutrophil infusion in this setting, a finding that may reflect their very short survival times in the circulation.

A workaround might be to use blood 'progenitor-like' cells, which possess the potential to persist, expand and then differentiate into mature neutrophils. We are exploiting new cell culture technologies to expand haematopoietic stem and progenitor cells to create novel 'off-the-shelf' blood products enriched for neutrophil progenitors.

As part of this work, we are considering how to clinically scale these methods so that they are compatible with good manufacturing practice guidelines and beginning to work out the health economics of such an approach. The same technologies used to expand haematopoietic stem cells could also represent an opportunity to generate other cell products, including those that have undergone gene editing; this sort of strategy might be used to correct mutated genes in cell transplants being used to treat inherited disorders of the blood or immune system. The expansion of stem cells may help to improve the efficiency of gene editing and the safety of transplants.

Theme 3: Patient-reported outcomes and health data

New chimeric antigen receptor T-cell therapies (CAR-T) are transforming management for some patients with leukaemia and lymphoma. While these treatments represent an important advance, there is emerging evidence that not all patient populations are accessing these treatments equally. To better understand why this inequality might occur, we are interrogating large-volume health data for the various intersectional and structural factors that could influence access to treatment and clinical outcomes. This information will also be important in informing how we measure the impact of CAR-T from a patient perspective and will help us to develop digital tools that improve interactions between patients and hospitals, for example by providing clinical alert functions.

Importantly, regulators are pivoting towards the use of these kinds of data as part of health technology assessments. The development of these new electronic patient-reported outcomes measures (ePROs) requires close engagement with patients and other stakeholders, not only at the initial design stage, but also later to assess usability and real-world operation. The rich data generated using ePROs is also providing new opportunities to use AI-based tools that better predict which patients require closer monitoring after CAR-T treatment.

Patient and public involvement and engagement

Our patient and public involvement and engagement (PPIE) group is involved across each of our themes and has a major influence upon research questions and prioritisation. A range of opportunities are offered to support choice and inclusion, including regular online meetings to discuss research and PPIE strategy, home-based activities to inform research input and co-produce outputs, and collaboration with PhD students via the Patient and Student Partnership framework.

To date, 25 public contributors have been actively involved, including patients with varied conditions, partners, parents and donors. The group also demonstrates diversity in occupational status and protected characteristics. Several have transitioned to leadership roles (e.g. co-chairing meetings or representing the BTRU in other meetings, including cross BTRU/NHSBT meetings). Joint planning of BTRU events, activities and outputs is now routine.

Examples of the approaches taken include participation in the project management group, regular meetings with BTRU researchers across themes, co-authoring peer-reviewed articles and newsletters, reviewing ethics applications, co-producing engagement materials and producing talking head videos.

Cross-BTRU collaboration

The BTRU in Precision Cellular Therapeutics is 1 of 5 BTRUs. The others focus on use of health data to inform transfusion practice, next-generation genomics to identify blood-borne pathogens, the use of new technologies to improve organ transplantation, and the development of new interventions to promote donor wellbeing. We are seeking to better identify the potential of working with the other BTRUs in relation to PPIE, behavioural science and ePROs.

Beyond this, our BTRU closely cooperates with other NIHR infrastructure (for example, the Biomedical Research Centres and Advanced Therapy Treatment Centres) to further the goal of accelerating equitable delivery of novel cell therapies in the clinic.

Meet the author

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