Integration of microfluidic approaches with cell therapy manufacturing through collaboration between academia and industry

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Cancer is a leading cause of death worldwide, with one in six people losing their lives to it every year. Haematological malignancies specifically are the fifth most common cancer diagnosis in the UK and the most common one in children. Over the last decade, we have witnessed a decline in cancer death rates and an improvement in treatment options and their effectiveness. However, the disease is still prevalent in the population and will continue to be in an ageing society, increasing the burden on already stretched healthcare systems. To reduce its impact, there is a need to develop effective therapies, resulting in durable responses, able to clear the disease rapidly and with minimal side effects.

Chimeric Antigen Receptor (CAR) T cells are a novel form of cancer therapy, in which a patient's immune cells are genetically reprogrammed to gain the ability to destroy tumours. This is an autologous approach, where cells used for the treatment come from the patient themselves (see *Figure 1*), as opposed to allogeneic, where donor cells are used to generate therapies that can be used for multiple patients. Genetic modification is achieved with the use of viral vectors, delivering the necessary genes into cells, which then express the chimeric receptor on their surface. When encountering a surface protein characteristic of tumour cells, modified CARs recognise it and subsequently trigger an immune response leading to cancer cell death. After the first regulatory approval of this type of therapy back in 2017, five more have been made available on the market, and hundreds of others are currently undergoing clinical trials. The commercial therapies all target cancers of the blood; however, CAR T cells aimed at other types of tumour are also being investigated. This interest in CAR T cell therapy development demonstrates its potential and gives hope for its implementation as a standard line of therapy.

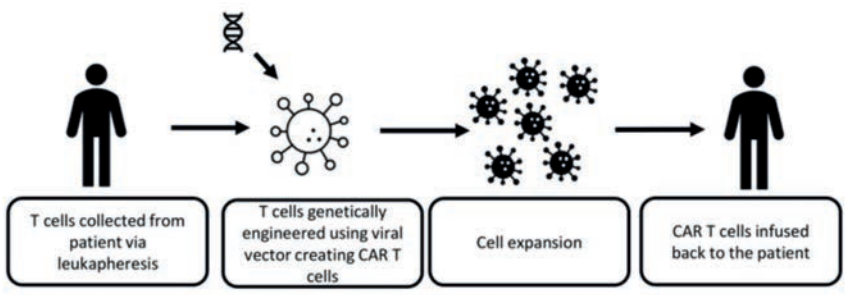

Figure 1. Autologous CAR T cell manufacturing.

Multiple hurdles must be overcome to make CAR T cells available to a wider patient population. The manufacturing of the therapy is a complex task, which involves shipping patients' cells to a centralised production facility for processing and stringent quality control assessment, both performed by highly qualified staff. Once released, the final product is shipped back to the hospital, where the therapy is administered. There is a limited number of large research hospital centres that offer this treatment during clinical trials, due to it being a novel and highly specialised medicine, which often results in long-distance shipments of the patient material or final drug product. Additionally, as the therapy can cause serious side effects, it is administered in an in-patient setting, adding to the financial burden associated with it. The combination of complex manufacturing, the need for highly qualified staff, extensive transport logistics and detailed safety requirements results in a high cost of the treatment, which ultimately restricts its availability to a wider patient population.

Automation of both processing and analytical equipment is key to lowering the cost of manufacturing and additionally has the potential to improve final product quality. Semi-automated bioreactors have been introduced into CAR T cell production; however, they still require regular operator interventions. Quality control is currently carried out separately; trained scientists perform the analytical assays required to inform of the product characteristics on samples removed from the production environment and processed on specialised equipment. To move to a fully integrated manufacturing process, quality control requires automation and integration with bioreactor systems. This is also recommended by the US Food and Drug Administration (FDA) as part of their Process Analytical Technology (PAT) initiative. When PAT is implemented successfully; it is capable of monitoring product quality as well as feeding back relevant data into adaptive process control. Once this level of automation is achieved, CAR T cell manufacturing can move to a decentralised model, where therapies are made at the patient's bedside, improving both their accessibility and cost.

In my role as a Process Engineer within the Process Development team at Autolus Ltd., a cell therapy company working to develop blood cancer treatments, I am responsible for the development and improvement of the CAR T manufacturing processes. It involves running multiple experiments to understand the source of variability and how to minimise it. To be able to gather all this information, I utilise a variety of analytical methods. These are often labour-intensive and involve the use of sophisticated equipment. In a research laboratory, using complex methods to fully characterise the product and identify its critical attributes is justifiable; however, once translated to the manufacturing environment, those methods require significantly more time and effort due to strict regulatory guidelines that have to be followed. This is why it is crucial to develop automated systems that measure the key cell characteristics reliably, yet without human intervention. Thanks to the generous funding provided by the Royal Commission for the Exhibition of 1851 (RC 1851), I am able to collaborate with an academic centre to address these issues and implement potential solutions in a commercially relevant manufacturing process at Autolus Ltd.

Specifically, my project is looking at the automation of the testing procedures that assess CAR T cell quality. To achieve this, I am working with a biochemical engineering laboratory at University College London (UCL) that specialises in developing microfluidic devices for cell culture applications. With its proprietary designs, they have developed an adherent cell perfusion system, capable of online cell culture monitoring. Through this collaboration, I can develop the engineering skills necessary to integrate cell analysis into a microchip and couple it with a detection method to obtain reliable results. The bioprocessing experience obtained at Autolus has provided me with an understanding of parameters relevant to CAR T cell production, which will allow me to develop a device tailored to the industry's needs. Some of those are quite different from what is typically measured in similar sectors, such as biopharmaceuticals (a branch of the pharmaceutical industry, focusing on the development and manufacturing of advanced drugs using biological systems such as cells), where the implementation of sensors has been successful in monitoring key parameters. To be able to develop useful PAT, it is necessary to understand the critical attributes of the product that define its quality.

For CAR T cells, cell surface marker expression levels are crucial to the efficacy of the therapy in patients and therefore must be measured. It has so far been achieved by utilising gold-standard methods adopted from research settings; however, these are often complex, manually operated and require extensive sample manipulation. These characteristics are not suitable for manufacturing, where results need to be acquired in a fast, reliable, and consistent manner, to ensure process parameters can be adjusted to achieve optimal process outcomes. The utilisation of microfluidic devices as analytical platforms allows tight control of fluids and low sample input to obtain relevant results, an especially important feature when dealing with precious patient material in an autologous setting. Additionally, microfluidics lends itself well to integration with detection methods necessary for parameter quantification. By automating this novel analytical system, results will be generated more rapidly, providing more accurate information on the process (closer to real-time), and thereby allowing more informed decision-making by the operators (which ultimately leads to improvement in the quality of cells in culture). It will also lay foundations for future work to implement algorithms capable of making decisions based on data obtained, taking the automation of the manufacturing workflow one step further.

The development of an automated analytical device and its implementation into a CAR T cell manufacturing process has the potential to drastically improve process consistency, and therefore ensure each batch produces a highly effective therapeutic product. This project is therefore part of an ongoing drive for automation and increased process control, which is aligned with the requirements of the vision of Industry 4.0. Additionally, it will reduce the need for operator intervention in sample preparation, manipulation and result analysis, decreasing the total cost of manufacturing, and therefore making these novel and potentially highly effective therapies more widely available.

In a novel and rapidly changing field such as cell and gene therapy, there is a need for efficient collaboration between world-leading innovators and the industry to ensure the most suitable solutions are directly translated into real-world applications. This implementation-based project will efficiently drive relevant innovation within CAR T cell processing to ensure these therapies are at the forefront of cancer treatment solutions. The Industrial Fellowship awarded by the RC 1851 enables me to establish this collaboration and lead a project directly relevant to the future of the industry, whilst training for a doctorate qualification in a world-leading academic centre. This benefits both my academic laboratory and industrial partner as it allows the exchange of knowledge and ideas, making research more relevant to the industry's needs and ensuring the implementation of novel solutions in a commercial setting. It provides the opportunity to test any prototypes on an existing clinical manufacturing process and compare it with current industry standards, whilst utilising research facilities and breadth of knowledge within the Biochemical Engineering department at UCL. Additional funding available for travel and conference attendance allows me to network within the field, deepening my understanding of the needs of the industry, and enabling further collaboration.

One thing seems certain: if the cell and gene therapy field is to become a standard cancer treatment, it needs to prioritise the implementation of novel technologies across the entire product life cycle, starting with new therapy development, through to production, all the way to supply chains and dose administration. Only such a holistic approach to drug discovery and implementation will lower the costs and enable faster regulatory approvals of the therapies, and ultimately lead to the health benefits mentioned for our society. With the 1851 Industrial Fellowship, I can both contribute to and be part of this venture.