Navigating the final mile: how are Australian hospitals delivering autologous cell & gene therapies?

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On October 9, 2023, David McCall, Senior Editor, Cell & Gene Therapy Insights, spoke to Sharon Sagnella, Research and Development Manager, Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, about overcoming the final mile to deliver autologous therapies to patients in Australia. They discuss the challenges hospitals in Australia face, and how they are developing the personalized supply chain capabilities to overcome them. This article is based on that interview.

BACKGROUND
Royal Prince Alfred Hospital (RPAH) is one of Australia’s oldest tertiary referral public health care institutions. The Department of Cell and Molecular Therapies (CMT) at RPAH is responsible for handling any cell and gene therapies (CGT) delivered to clinical patients. This may involve storage and infusion of products, complex formulations, and cell manipulation. At present, CMT is servicing 12 active CGT clinical trials with around 11 new CGT trials in the pipeline that are earmarked to begin within the next 12 months. Indications span a number of different clinical departments including hematology, neurology, oncology, and cardiology. CMT comprises four GMP cleanroom suites, a production team, a quality team, a clinical trials team, an operations and administrative team, and a research team for process development and translational projects (approximately 20 staff members). In addition to servicing clinical trials, the department is responsible for the delivery of Yescarta and Kymriah, the two approved and funded CAR-T therapies in Australia. Furthermore, CMT provides clinical CGT manufacturing capabilities to clinicians, academics, and industry partners.

CAR-T therapies are available at six different locations in Australia including RPAH, Royal Brisbane Hospital, Sydney Children’s Hospital, Westmead and the Children’s Hospital at Westmead, Peter MacCallum Cancer Centre, and the Royal Children’s Hospital. In addition to Kymriah and Yescarta, Tecartus and Carvykti are Therapeutic Goods Administration (TGA)-approved.

THE FINAL MILE IN HOSPITAL SETTINGS
A fastidious approach and planning are necessary for the implementation of CGT in a hospital setting due to the complexities of delivering this type of specialist service. This approach must be multi-disciplinary with dedicated funding to meet clinical, scientific, logistical, and regulatory requirements. Hospitals require specialist cell handling capabilities including proper infrastructure and trained staff to meet the necessary regulatory requirements. An accredited apheresis unit is an essential component for the delivery of a range of cellular therapies. Furthermore, clinical expertise spanning a range of specialties with direct experience in managing patients receiving CGT is also required.

CMT has been a pioneer in the clinical implementation of CGT having been involved in the first gene therapy clinical trial in 2001 for the treatment of hemophilia which utilized AAV delivery directly to the liver. Building of the CMT cleanroom facility at RPAH, a vital piece of infrastructure for the future service delivery of CGT, was completed in 2012. RPAH was approved for the provision of CAR-T cell therapy service in 2019 and the last three years have seen a large uptick in service delivery due to the steady increase in CGT clinical trials.

CMT in consultation with RPAH Pharmacy, RPAH institutional biosafety committee, and RPAH research and governance office has a set of guidance documents provided to RPAH clinical departments on how to implement CGT in the clinic. The first stage of that process is consultation with CMT to ensure that the necessary
infrastructure and trained staff are available to feasibly service the clinical trial. This involves a number of considerations including the number of patients expected to be on a trial, the cold storage requirements, formulation requirements, additional onsite manufacturing requirements, etc., thereby ensuring the resources, including staff, are available to handle the trial. This process has become more essential in recent years due to the large uptick in the number of CGT clinical trials in the pipeline worldwide.

Once a trial is considered feasible, it must go through regulatory approval. In Australia, if the trial involves a genetically modified organism (GMO), the sponsor or commercial entity must establish if they require a GMO license from the Office of the Gene Technology Regulator. Institutional Biosafety Committee applications may be required through the specific site in addition to human research ethics approvals before a site-specific application can be submitted to obtain final research governance approval to conduct the clinical trial at RPAH.

Staff involved in the trials must complete the required training in investigational product handling and storage conditions. Chain of custody must be maintained from the product’s receipt on site until it goes into the patient. This process involves a great deal of logistics, communication, and adequate staffing. Additionally, extensive documentation is required to demonstrate all processes and procedures have adhered to the product handling specifications and that chain of custody has been properly maintained throughout the delivery of the CGT.

CHALLENGES FOR AUSTRALIAN HOSPITALS IN DELIVERING CGT

Currently, one of the major issues the CGT field is facing is the trained workforce gap. Public hospitals are limited in staffing numbers, and the CGT pipeline is ever-increasing. In Australia, and around the world, there is a small pool and pipeline of experienced staff who are able to do the work, including experienced clinical staff who understand the clinical management side of CAR-T therapies and the challenges that come with delivering those. This is in addition to the lack of trained technical staff responsible for handling, manipulation, and formulation of CGT under GMP-compliant processes.

Three years since service delivery of Kymriah began in 2020, the clinical hematologists at RPAH have now treated more than 80 patients and are well experienced. In other parts of Australia, that experience is limited. A lack of trained, experienced workforce poses challenges to every aspect of the logistics pipeline. There are no training programs in universities for training the CGT workforce at present; most training happens through well-developed in-house training programs. Furthermore, the management of CAR-T and other CGT by clinical staff is not necessarily something that would be covered through their basic training.

Chain of custody of the product also poses challenges, as each sponsor has their own software or system. Some of the smaller ones still remain paper-based. Every time a new trial is taken on, staff require training for each new product and the procedures are never the same from one trial to the next. By next year, RPAH is expecting to have two dozen trials ongoing, and each of the seven production staff will have to be trained in all processes involving receipt, storage, processing, and formulation for infusion.

Yet another challenge in Australia is the distances existing across a big country. There are a limited number of places that can realistically deliver these types of therapies to patients. Reaching the patients living in more rural and remote places to deliver therapies is a specific challenge within Australia.

Other challenges in Australia in CAR-T and other CGTs are based on a reliance on offshore manufacturing. All commercial therapies are currently manufactured offshore, and there is limited availability of manufacturing infrastructure for CAR-Ts
or cellular therapies in Australia. There are a handful of smaller facilities, including RPAH, and a couple of larger ones, but capacity remains a challenge. Another challenge is the high costs of CAR-T therapies and other CGTs and how to best be able to provide these through a public health system. The federal government must find pathways to fund these into the future. For example, while there are four TGA-approved CAR-T cell therapies in Australia, currently, only two are funded. As a way to manage the high cost of these therapies and ensure the right patients receive them, a national steering committee meets on a regular basis involving clinicians from CGT-qualified centers. If a clinician wants to place a patient on one of these therapies, it must be discussed and decided by a multidisciplinary team across the nation.

As the CAR-T field moves towards solid tumors, the issue of funding in Australia will become more pertinent. A hemophilia B gene therapy has recently been approved by the TGA, with a price tag of approximately 5 million AUD. The Australian government needs to have discussions and make some tough decisions about funding these types of therapies going forward. Hopefully, they will become cheaper, but they will always be more expensive than a small molecule or biologic.

CGT REGULATION IN AUSTRALIA

Australia regulates gene-based therapies via the Gene Technology Act 2000 and the Therapeutics Goods Act 1989. The Australian regulatory system is unique in that it has a centralized regulator—the Office of the Gene Technology Regulator which strictly regulates GMOs in Australia. Cellular therapies in Australia are regulated as biologics, while gene therapies are regulated as prescription medicines by the TGA. Biologics can be classified as class 1–4, with CAR-Ts classified as ‘high risk’ class 4 biologics. TGA approval for conducting clinical trials in Australia can occur via two different pathways: clinical trial notification and clinical trial approval. Clinical trial notification is used for therapies that have already been approved by a different regulatory body, such as the US FDA or EMA. This is simply a notification to document that a product is going to be used in a trial. The clinical trial approval pathway is a more complex full application process that is needed if using a therapy that has not previously been used. This is similar to the IND in the US. Approval of a product for commercial use requires an extensive review process by the TGA to assess safety, quality, and efficacy.

DEVELOPING SUPPLY CHAIN CAPABILITIES TO HANDLE AUTOLOGOUS CGT PRODUCTS

Access to GMP vectors in Australia can pose difficulties. There are no companies within the Australia and New Zealand region at present that can produce GMP vector, with the closest being in Singapore. GMP vector is in high demand, and not having it within the region has been a barrier to much development. Hopefully, next year GMP manufacturing will be available in New Zealand. In addition, a vector manufacturing facility is being built at Westmead but is still awaiting its GMP license.

As the move towards more onshore manufacturing takes place, the question of booking spots in manufacturing will be raised. A few centers have GMP licenses for CAR-T manufacturing already. Having centers work well in conjunction with each other would be ideal, but unfortunately, a lot of state-to-state competition is seen in the country, creating unnecessary barriers.

As only six hospitals in Australia have been approved and qualified for the delivery of commercial CAR-T cell therapies, there is a large portion of Australia that must travel long distances for access. The logistical challenges posed by moving these therapies around are huge. Moving towards a hub and spoke model with other hospitals could help
address some of these challenges, however, more trained technical and clinical staff will then be required.

Another change is a push towards point-of-care manufacturing, which many hospitals are looking into. This could be beneficial, but it may take a while before the field is ready. In addition, there are continual technological advancements in the manufacturing processes and software that will bring down the cost of these therapies.

The COVID-19 pandemic highlighted many difficulties in Australia’s reliance on overseas. A lack of production onshore means an increased frequency of supply chain issues, such as from the standpoint of getting technicians into service facility equipment or replacing equipment parts as well as access to necessary consumables. Due to Australia’s location, it has the unique challenge of supply chain vulnerability.

LOOKING TOWARDS THE FUTURE OF THE FINAL MILE

It is hoped that processes and procedures can be standardized along the logistics chain in the future to ease implementation. Differences in software and quality control tests can be tedious. Standardization can help at every step of the process.

In CGT, there will likely be a move towards more allogeneic therapies, with less reliance on autologous. Allogeneic is still in its early stages, but this would remove some of the logistical steps, including apheresis, and allow us to move more quickly. It is unlikely that autologous therapies will entirely disappear, but a reduction in reliance on them is likely.

In the CAR-T therapies, other immune effector cell types continue to be explored, including natural killer cells and $\gamma\delta$ T cells. There is a huge range of different types of immune effector cells, each with various benefits. These could be more allogeneic, in that they can be created in batches without the requirement for manufacturing slots for each patient.

A recent push within New South Wales to standardize the hospital pharmacy requirements has occurred. They are beginning to put out guidance for hospital pharmacies for handling and delivering CGT products to the clinic. This is not yet Australia-wide, but it is a step in the right direction.

More guidance from the people on the ground is needed. Dr Sharon Sagnella and Professor John Rasko participate in a number of steering committees relating to CGT implementation at RPAH. In a decade, the field will hopefully have identified ways to improve access in Australia to rural and remote communities, which is one of the biggest challenges. Ensuring equitable access to these therapies across Australia, including many remote Indigenous communities, remains a priority.

BIOGRAPHY

SHARON SAGNELLA is the Research and Development Manager for the Department of Cell and Molecular Therapies at Royal Prince Alfred Hospital, Sydney, Australia. After completing a PhD in Biomedical Engineering at Case Western Reserve University, Cleveland, Ohio, she gained extensive experience in process development and commercialisation during time spent in CSIRO and industry. Throughout her career, she has contributed extensively to preclinical development, clinical trials, and the clinical implementation of new therapies.

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