CROSSING THE VALLEY OF DEATH

Guidance for Researchers Translating a Research Discovery into an Advanced Therapeutic Product

Key messages:

- *It is never too early to reach out to the facilities within **TIA's Cell & Gene Therapy Capability** for advice on making the transition from research to development.*
- *Early engagement with TIA or one of the facilities will enable you to leverage their significant expertise and expedite your translation to clinical development.*
- *Understanding GMP requirements early will save you time and money.*

The development and manufacture of cell and gene therapies is highly complex. It is also a rapidly growing industry, with the global regenerative medicine market estimated to reach AU$120 billion by 2035 (1). There is an extensive collection of cell and gene therapies that have been approved for use in Australia and overseas (2). This potential has resulted in considerable research effort in academic research labs, with ~1200 researchers employed in regenerative medicine groups/labs across Australia (1). Within Australia the academic research community has interests across the whole spectrum of cell and gene therapies, including novel gene therapies for rare diseases, cellular therapies for solid tumours, viral and non-viral vectors for cellular therapies and *in vitro* tissue regeneration.

However, Australia suffers from a well-recognised impasse in translation of academic research to clinical testing, sometimes referred to as the "Valley of Death". Crossing this valley, especially to reach an outcome of clinical supply of a cell or gene therapy, can be daunting**.** The high cost, regulatory burden and technical challenges make this transition a very difficult road, but there are resources and expertise available from established R&D groups who have already travelled this road, and can pass on their expertise and advice in the early stages of planning as well as assisting with process development for clinical grade manufacture.

TIA's **cell and gene therapy capability** is a consortium of the five centres in Australia with TGA-licensed GMP manufacturing for cell and gene therapies. They include:

- Cell and Tissue Therapies, WA (CTTWA)
- Cell and Molecular Therapies (CMT) at Royal Prince Alfred Hospital
- Peter Mac Centre of Excellence for Cellular Immunotherapies
- Q-Gen Cell Therapeutics
- Sydney Cell and Gene Therapy (SCGT) at Westmead Health Precinct

Together, these centres offer the full range of manufacturing capabilities across the cell and gene therapy landscape.

Our Mission

Therapeutic Innovation Australia's (TIA) Cell and Gene Therapy capability has been established to enable and accelerate the translation of research discovery along the therapeutic development pipeline by ensuring world class research infrastructure facilities are accessible to the Australian translational

Enabled by NCRIS National Research Infrastructure for Australia An Australian Government Initiative

research community. The capability is a consortium of the five TGA-licenced, public-sector GMP facilities for cell and gene therapies (3). **Early engagement with TIA or one of the facilities will enable you to leverage their significant expertise and expedite your translation to clinical development**.

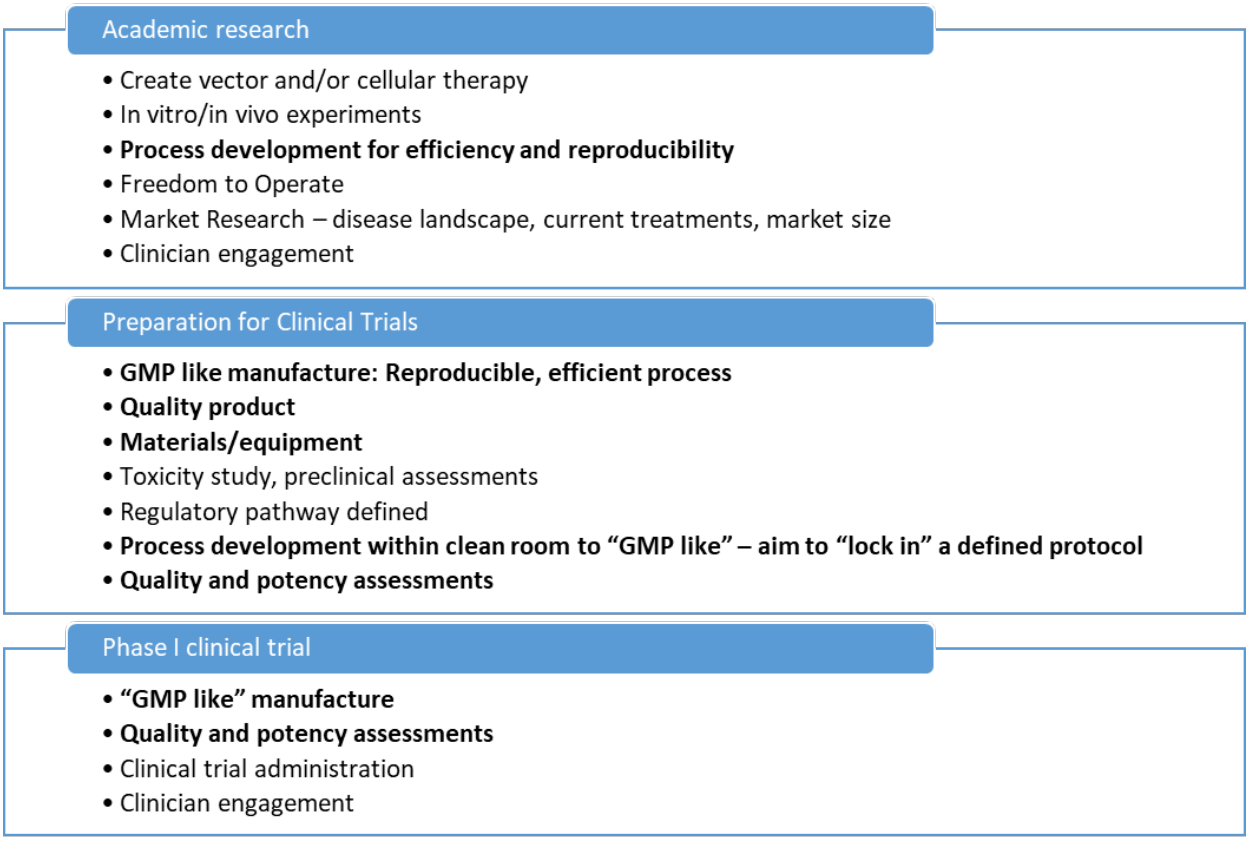
"Cell and Gene Therapies 101"

There are many questions that will need to be answered during drug development. While they don't all need to be answered immediately, some awareness of them will be beneficial when speaking with a development/manufacturing partner. Broadly speaking, these fall into three categories:

1) Technical questions
2) Regulatory questions
3) Business questions

This document focuses mostly on the technical questions, to help you be better prepared for translating your lab-based research to clinical grade manufacture in preparation for clinical trials. These technical questions are specific (but not unique) to the cell and gene therapy industry. These are the considerations that can mean the difference between an academic invention and lifesaving drug. It is therefore fundamental that these technical questions are addressed before initiating clinical trials, whilst the regulatory and business questions may occur at any/all stages of development (Figure 1).

*Figure 1: Early Engagement with TIA's Cell and Gene Therapy Capabilities will improve your drug development pathway. Areas that TIA capabilities can assist or advise are highlighted in **bold** font.*



Technical Questions

"What is GMP, and do I need it?"

One of the main differences that researchers encounter when starting to think about clinical grade products is the concept of Good Manufacturing Practice (GMP). Whilst manufacture under TGA-licenced GMP conditions is technically ***not*** required for the first in human clinical trial, manufacture of test items will need to be "GMP-like". Laboratories and facilities that have received a licence for GMP manufacture from the Therapeutic Goods Administration (TGA) have been through a very stringent validation, qualification and quality control process that includes the people, processes, equipment and consumables. For this reason, you probably won't want to be getting your own lab to be certified or licenced to a GMP standard, as it may restrict your discovery research.

Even though you are unlikely to need GMP certification for your lab, you should focus on ensuring your product and the process to produce it are as ready as can be for clinical grade manufacture by considering the following.

Firstly, manufacturing a cell or gene therapy for a mouse will not necessarily transfer easily to manufacturing for a human patient. You need to look at all stages and materials used in your product manufacture to ensure that they are suitable for human use, including for example the choice of media, reagents and plastic consumables.

Secondly, manufacture of therapeutics is heavily integrated with extensive quality control. The product needs to fall within predetermined quality parameters that must be achieved prior to patient administration. During clinical manufacture, every step of the process will need validation and quality checks that ensure the product meets quality standards. For example, for CAR-T cells the transduction efficiency, the number of cells and ratio of cell types are some of the indicators of product quality. Because these products rely on patient cells that are highly heterogeneous, the manufacturing processes need to be robust and reproducible to minimise fluctuations in quality of the end product.

Good Manufacturing Practice

Good Manufacturing Practice is a set of principles and procedures that, when followed, helps ensure that therapeutic goods are produced to a high quality. Quality must be built into each batch of product during all stages of the manufacturing process. The GMP process includes training and validation of personnel, qualification and monitoring of the facility and the equipment, qualification and control of raw materials and consumables, validation of processes and quality control and inspection by the relevant authorities. The Australian code for GMP for human blood and blood components, human tissues and human cellular products can be found on the TGA website

And finally, although your therapy does not need to be fully GMP-compliant for the first in human phase I clinical trial, it will need to be for subsequent phases. If your manufacturing process needs to be rebuilt between Phase I and Phase II because of non-GMP compliance, then you will likely need to repeat your Phase I trial. So it makes sense to put GMP-like manufacturing in place for Phase I, to ensure easy transition to Phase II. Developing GMP compliant manufacture prior to your first phase I may seem expensive and slower in the short term, but you will be so much better prepared for future studies. **It will ultimately save you time and money.**

"What questions do I need to consider now?"

Early engagement with TIA's cell and gene therapy capabilities will help you to build a framework for manufacture, including embedding GMP-like methods into your research plan, even as early as preclinical testing. TIA's cell & gene therapy facilities have highlighted some key questions that will need answering as part of the preclinical work up of your product. The facilities may be able to offer assistance in answering these questions but you should definitely be aware of them in very early stages of drug discovery.

- Are you using a suitable viral vector?
    - Not all viral vectors will be appropriate for use. For example, lentiviral vectors may report false positive HIV results (3) whilst pre-existing immunity to adenoviral vectors may restrict efficacy (4).
    - There are multiple adeno associated virus (AAV) serotypes. In particular, the capsid proteins have different tropisms to different organs (5). For example, if you are considering a therapy for a neurological condition, then you would want to choose a neuronal tropic serotype. Or, if you are concerned about liver toxicity, you would choose a different serotype that is non-hepatotropic.
    - Generally, AAV vectors are better suited to *in vivo* gene therapies, whist lentiviral will be better for ex vivo manipulation (such as CAR). What is the rationale for use of the vector you have chosen?
- What titre of vector will you need? How do you know it is active? What batch tests do you need to perform to ensure that you have a vector of sufficient activity?
- What is the providence of any cell lines you are using? Are they suitable for human use? What is your source of cell line? Do you have permission to use them for drug development? Do you have suitable donor consent for allogeneic cells (eg pluripotent stem cells, mesenchymal stem cells)? Do you need to establish an agreement for potential commercial use? For example, you may be able to use them in exchange for a percentage of income or similar arrangement (rather than paying a far higher fee up front).
- What culture media are you using? If it is research use only (RUO), how easy will it be to transfer to GMP grade?
- If you are performing *ex vivo* manipulation of cells, how are you isolating your cells? Some companies have both RUO and clinical grade products. For example, Dynabeads are available either as RUO or cell therapy system (CTS), simplifying the transition from research to clinical grade.
- Are you using supplements for cell culture? If so, are they suitable for use in humans?
    - Serum – generally you can't use foetal calf serum or other serums in preparations for human use
    - Cell stimulators – what is an appropriate stimulation method for clinical manufacture? For example, for T cells you may be using RUO interleukin 2, but aldesleukin is an IL-2 drug approved for use in melanoma, so are you able to use this for your stimulation?
- What are the parameters you are willing to accept for cell number, purity etc? You may need to provide a reference range for which you are willing to work. This will need to be based on reasonably reproducible levels. Remember, that for patients, this may be the last available treatment option and they may be very sick, so it may not be possible to obtain high numbers of cells, and you need to be able to treat near to 100% of patients who enrol onto a study. But if you set you acceptance parameters too high then many patients may not be able to meet the acceptance criteria.
- How many steps does your process have? Over time, you will want to reduce the number of steps to reduce contamination or errors. What mechanisms are available to do this? For example, can you look at closed systems for cell isolation and activation?

- How many testing points do you have in your process? The frequency and breadth of testing will impact time and cost of production. Are you able to define your product with fewer markers? Which days are crucial for testing (every day, defined days or decision days?)
- Do you know how your product is having its desired effect? What is the active constituent? For example, in a CAR-T therapy, is it the CD8s or also CD4s?

Regulatory Questions

It is important to prepare a clear clinical plan from the outset. This is a large undertaking and you are strongly advised to engage with TIA's cell & gene therapy capabilities, who will be able to advise on regulatory issues based on their experience. You will need to identify which regions you are looking to initiate clinical trials and also the jurisdictions in which you'll be looking to seek regulatory approval. There may be different requirements for the different regulatory authorities in the regions you are targeting. Some of the important questions include:

- What preclinical data is required to initiate a phase I in Australia vs. US or EU? For example, Australia is creating a niche for early initiation of phase I trials, but the US Federal Drug Administration (FDA) still requires trials to be performed in US.
- Do you need to wait until all the preclinical data is in place before moving to clinical? Or are there some results that can be done in parallel?
- How many Phase I trials will you need to do? The main purpose of a phase I is to show safety, but increasingly there is an element of efficacy included. Which patients are most likely to obtain benefit? Should the phase I include only these patients or expand out to larger pool of patients?
- What data will you need to move to phase II?

Business Questions

Intellectual property (IP)

You must know who owns or has claim to IP associated with your product. Your own personal IP position in a product is also crucial information and may depend on the conditions of your employment. Collectively this is known as Freedom to Operate (see right).

Most universities and research institutes have a technology transfer or a commercialisation office and you should approach them as early as possible for them to guide you through the process of developing an IP strategy.

Freedom to Operate

Freedom to Operate is the ability to commercialise a product without infringing on any copyright or intellectual property rights. This would include licenses to use GMP packaging cells, plasmid construct, transgene and/or transgene expression cassette. If you are starting a new company then you may need to negotiate a licence from your previous employer to use your invention for commercial or development purposes.

Market Research

Drug development is very expensive, and successful translation will require significant investment. Your product will need to be attractive to potential investors, many of whom are being pitched novel and exciting potential therapies on a daily basis. And while they may not understand the science as well as you, they will know the market. You will need to demonstrate that their investment in your discovery has

the potential to generate a significant return, such as improved patient benefit, health system cost savings, and commercial income from sales or licencing.

Potential investors will want to see specific market insights including:

- What is the disease burden (number of patients, lives lost etc) and current treatment?
- What other drugs are in development for this disease?
- What will your drug be competing against for market share if you get to approval? Manufacture of cell and gene therapies is much higher input than other therapies, so you will need to show that your drug will significantly improve the current treatment paradigm to be able to justify the cost.
- One time cure vs lifetime of treatments – which is more cost effective? If your drug will cure a patient in one go and thus reduce the requirement for continual hospital visits/stays then it may be more cost effective to the health system than the cheapest alternative drugs.

You will also need to think about how much investment you will need at this point, and what level of control you are willing to give up. Just as your time in the lab goes down as your career develops, the level of control that you have over the development of your invention will inevitably reduce as you go through the development process. If your product goes all the way to commercial supply then you won't still be making it in the lab each time, so you'll need to prepare for a staggered releasing of day-to-day operations as your product hits each milestone.

Are you ready to take a giant leap (or a small step)?

It is both exciting and daunting to be at the point of progressing your potential therapy out of the research lab and into clinical development. Hopefully, the questions posed in this document will have been helpful, but **it is never too early to reach out to TIA's Cell & Gene Therapy capabilities for advice on making the transition from research to development**. They have been through what you are going through and overcome many of the same challenges you will likely face. Developing your processes in consultation with clinical manufacturing experts will help you prevent some common mistakes, help streamline your processes and save money and time.

Further information/ Contacts

If you would like to discuss next steps in your product development, then please contact Heather Donaghy, the scientific engagement manager at TIA who will be able to guide you through the initial stages: info@therapeuticinnovation.com.au

References

1. Regenerative Medicine: Opportunities for Australia [Internet]. MTP Connect; 2018. Available from: https://www.mtpconnect.org.au/Attachment?Action=Download&Attachment_id=104

2. Alliance for Regenerative Medicine. Available Products [Internet]. [cited 2021 Apr 9]. Available from: https://alliancerm.org/available-products/

3. O'Sullivan GM, Velickovic ZM, Keir MW, Macpherson JL, Rasko JEJ. Cell and gene therapy manufacturing capabilities in Australia and New Zealand. Cytotherapy. 2019 Dec;21(12):1258–73.

4. US Food and Drug Administration. Package Insert - Kymriah [Internet]. [cited 2021 Apr 12]. Available from: https://www.fda.gov/media/107296/download

5. Zaiss AK, Machado HB, Herschman HR. The influence of innate and pre-existing immunity on adenovirus therapy. J Cell Biochem. 2009 Nov 1;108(4):778–90.

6. Lisowski L, Tay SS, Alexander IE. Adeno-associated virus serotypes for gene therapeutics. Curr Opin Pharmacol. 2015 Oct;24:59–67.