Cell and Gene Therapeutics: Translation from Discovery to Market

Key messages:

- *Translation of your product out of the lab and into clinical development will require a shift of mindset from research curiosity to process reproducibility*
- *You will need a robust, reproducible manufacturing method for tech transfer to a GMP grade facility*
- *The quality, safety and efficacy of the product will be interrogated, defined and documented during translation and tech transfer*

A checklist for translating a therapeutic candidate to a commercial product

This guidance document is for researchers in academia or start up biotech companies looking to develop a novel cell or gene therapy for commercial markets. This guidance checklist is designed to raise awareness of some crucial questions you'll need to be able to answer to successfully initiate clinical trials and subsequently bring your therapy to market. It has been developed through conversations with manufacturers, consultants, and drug developers to address practical translation knowledge gaps. If you've spent years in the lab developing what you hope will be the next blockbuster treatment for your disease of interest, then read on. You may already have some understanding of the relevant intellectual property, your freedom to operate, the unmet need and the potential market of your product[1], however the process of developing a novel cell or gene therapy is different from that of other therapies for several reasons:

1) Treatment tends to be personalised for an individual, so a successful therapy will need to *scale out* to manufacture batches in parallel, rather than *scale up* for larger batches.
2) The manufacturing process is typically integral to the efficacy of the therapy, and so ensuring this is robust and reproducible is necessary.
3) The starting material (patient cells) is not uniform and so managing the release specifications of the end-product can be troublesome.
4) It is harder to identify the specific components of a cell/gene therapy that are providing therapeutic benefit (due to the heterogeneous nature of the end-product).

TIA's **Cell and Gene Therapies Capability** is a consortium of the five centres in Australia with Good Manufacturing Practice (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 manufacturing capabilities across the cell and gene therapy landscape.

When thinking about translation activities from development to the clinical stage there are three main areas to focus on: manufacture (further broken down to product development, tech transfer, process development and clinical manufacture), regulatory requirements and clinical trials (Figure 1). They are very much inter-related, with some of the questions spanning multiple stages.

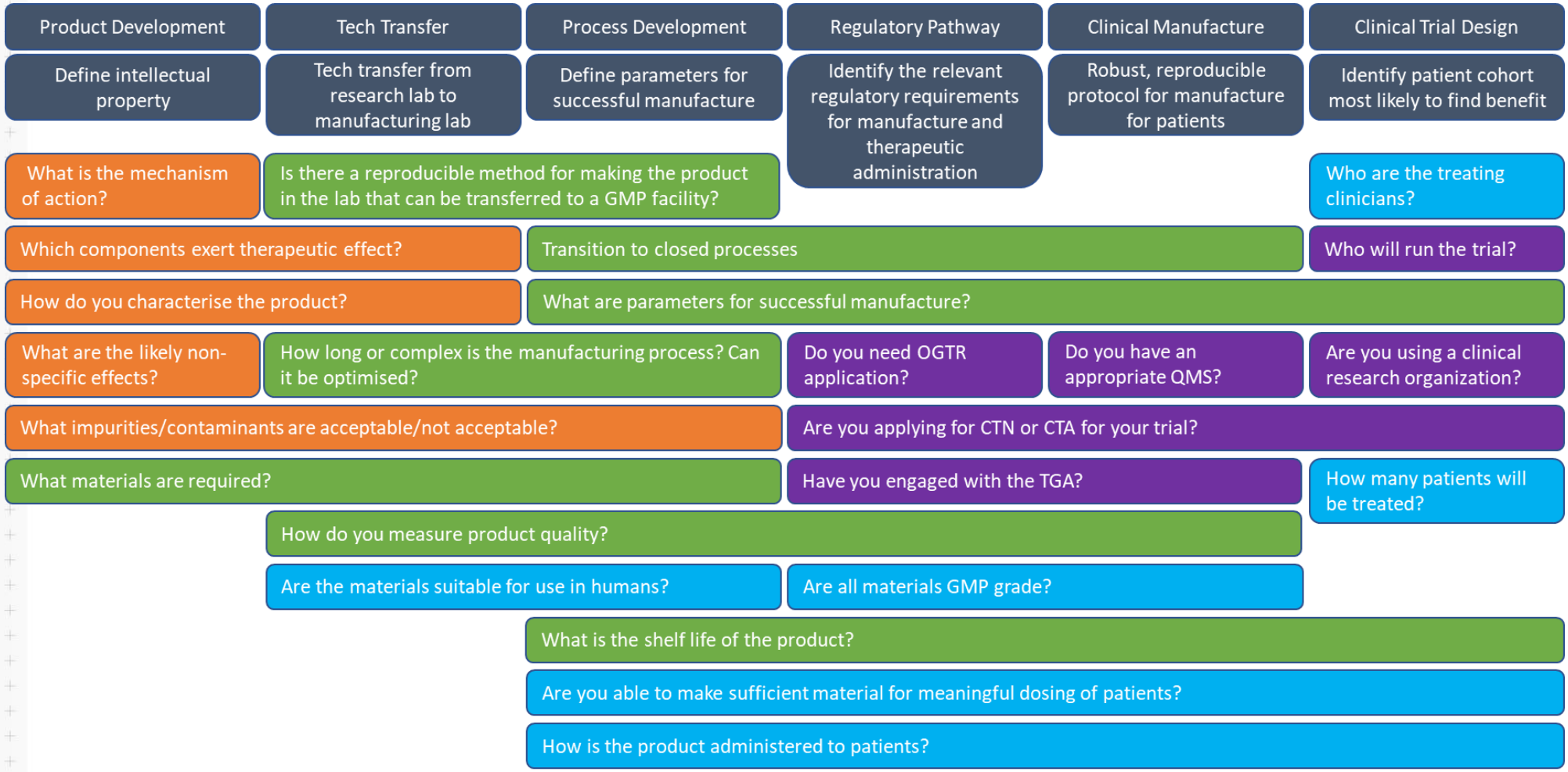

Figure 1. Checklist of questions to consider for commercial development of a new cell/gene therapy
Orange, relates to the product; green, relates to the manufacturing process; blue, refers to patient requirements; purple, refers to documentation requirements. CTA, clinical trial approval; CTN, clinical trial notification; GMP, good manufacturing practice; OGTR, office of the gene technology regulator; QMS, quality management system; TGA, Therapeutic Goods Administration.

Manufacture

It is important to understand the difference between **product development** and **process development**.

- **Product development** is the preclinical work that you do to ensure that you have a product with well-defined characteristics. When transitioning the process from your lab into a manufacturing facility there will be an expectation that most of the product development has already occurred.
- **Process development** involves the process optimisation and establishing consistency around manufacturing to support clinical use. This streamlining aims to reduce manufacturing time and cost of goods and improve reproducibility and safety.

For cell therapies in particular, this will likely affect the ability of your product to become an approved therapy that is listed on the Australian Register of Therapeutic Goods (ARTG). Clinical manufacture of a product requires in equally important parts the making of the product and in generating the data package of quality control testing that confirm what you state is in the product. Some of the key questions that your manufacturing partner will ask are captured below. If you can answer these, then you'll be on your way towards having a product ready for clinical manufacture. They will also form part of your submission to the regulatory authorities for approval to initiate clinical trials.

What is your product?

You need to know what components of your product have the therapeutic effect. This is important when dealing with preparations that may have different cell types or have different expression levels. Which cells are exerting an effect? What tests do you currently use to identify the components of your product?

Do you have a tried and tested protocol for making it?

The manufacturer will need to tech transfer your current process to their facility and reproduce your current methods before being able to develop it for clinical manufacture. You will need to provide very detailed protocols, ideally approaching Good Documentation or Good Manufacturing Practices (GMP). Details should include the brand of media and supplements, the concentrations and volumes added, temperature considerations, plasticware requirements and specific equipment used. You will need to have a robust protocol, one that can be repeated multiple times EXACTLY the same way. If you can show that you can repeat the manufacturing process in your lab, this will make it easier to transfer to your manufacturer's clean rooms. The manufacturing partner may suggest alterations and improvements, but they will expect you to have a defined process.

How do you characterise your product?

What are the key attributes for your product? What cellular phenotype, level of gene expression or transgene activity are needed for your product to have efficacy? What tests do you do to ensure that your product is what you're expecting? And what tests do you do during manufacture to ensure that the process is running smoothly?

What impurities/contaminants are acceptable/not acceptable?

You will also need to show the impacts of impurities or contaminants on the product. I.e., what are the acceptable limits for cell viability and purity or transduction efficiency, and what is the impact of residual reagents (e.g., beads), dead cells, protein or DNA on the efficacy of the product? If you have any data demonstrating the impact of lower purity, this may help to determine the acceptable parameters for your manufacturing runs. For example, you may have experienced 90% purity every time you've done your experiments, but what is the impact on your product (and/or assays) if you only have 60, 70, 80% purity? How many cells do you need to exert an effect? If you've always performed your experiments with one concentration of cells, what impact will fewer cells have on the efficacy? Remember, many of the patients that you will be looking to treat will be very sick, and this is their last treatment option. For autologous therapies, sick patient's cells are unlikely to produce uniformly optimal results, so if your acceptance criteria are too tight then this will have a huge impact on the patient. But knowing the limitations of your product will help to widen the limits for manufacturing acceptance.

If you're developing a gene therapy, you will need to consider the viral titre that you can achieve, but also the ratio of empty viral vector particles and vector integrity. What impact do the empty particles have on anticipated efficacy? You may need to balance yield over purity to be able to produce enough product for patient administration. What level of empty particles is acceptable in your system? Is there any aggregation of material at different concentrations? What other contaminants remain in your vector preparation after purification steps and what impact will these have on the efficacy of your treatment?

How does your product work?

You'll need to articulate the defined mechanism of action of your product, with sufficient *in vitro/in vivo* work to support it. It is likely that your experiments in the lab can go some way to providing this information. At this point however, as you approach clinical manufacture, it is important to develop or establish assay(s) that can show that the product has the desired effect, and that the effect is specific. These are often called efficacy or potency assays. The models that you use need to be relevant for the disease you are hoping to treat. If you want the therapy to be effective, you will need to be confident of these non-clinical data. Your experiments will need to be rigorous, reproducible and often blinded with appropriate controls.

What are the likely non-specific effects?

If you have a biological target for your product, what are the expression levels in normal cells? Even low-level expression can cause side effects, which you will need to have identified as potential adverse reactions and have mitigation plans. Do you need to consider co-administration of any drugs to limit these side effects?

What materials do you use in manufacture of your product and are they suitable for human use?

First, you'll need to identify all the materials (supplier, catalogue number and even batch numbers) that you use when making your product. This is needed for the tech transfer to the manufacturing facility, and to ensure they can source appropriate GMP -suitable equivalents of everything that you use. If you've had different effects with different batches of the same product or with different suppliers, that will be important information. Your product may be very sensitive to changes in media or supplements, so it may be wise to switch to materials produced according GMP as early as possible. This will be beneficial and avoid having to change your manufacturing process upon tech transfer to the GMP manufacturer, which may adversely impact product characteristics and/or performance. For Phase I clinical trials, a GMP manufacturing license is not mandated by the Therapeutic Goods Administration (TGA) but all materials for manufacture will need to be suitable for use in humans. For example, you won't be able to use any animal products (such as foetal bovine serum). Phenol red (found in media) is an irritant and so must be avoided at any stage of your manufacture.

How long does it take to make your product?

This will have a big impact on the feasibility of your clinical trial. There is currently quite limited capacity for manufacturing cell and gene therapies in Australia, with only 49 clean rooms across 10 sites[2]. Generally, only one process (one product) can be performed at a time in each clean room, limiting the capacity of manufacturing. For autologous cell therapies, this means that only one patient sample can be manipulated at a time. If it takes 28 days to manufacture and you are planning to treat 12 patients in your phase I trial, then this effectively means that it will occupy one clean room for an entire year to perform your study. If, however, your process is only 14 days duration and you have a good source of patients that can be recruited, then you could reduce the clean room occupied time down to 6 months. For allogeneic products, you are still only able to have one process at a time, but this may create a batch that can treat multiple patients, significantly reducing the clean room time required.

Also, don't underestimate the impact of the number of hours of operator, and lab space time, on costs. Have you considered ways in which you could reduce the handling and manipulation? The nature of GMP manufacture requires multiple additional steps such as gowning, material handling, cleaning before and after each process, environmental monitoring, in process testing, and documentation. These steps all add up, such that a simple media change that would take about 30 mins in a research lab may take up to 5 hours to perform under GMP. Transitioning to closed or automated systems will further reduce the time

that a person needs to spend making your product, which may save thousands of hours of clean room facility and operator time as well as importantly reducing errors and risk to the process reproducibility. These sorts of considerations may make the difference between the product being financially viable upon manufacture under GMP.

How do you define a successful manufacturing run?

Using the data from your characterisation assays, impurities assessments and efficacy/potency assays, you should now be able to define specific parameters and the acceptable ranges within which your product must fall to be suitable for use with patients. Without making any changes to your manufacturing runs, how often are you able to achieve these parameters? And if you are intending to use autologous patient samples, does this impact the variability such that it is difficult to manufacture products within the defined parameters?

How is the product administered to patients?

You will need to consider many aspects around how your product will be given to the patient. For example, it may be intravenously administered, but what volume or dose does the manufacturer have to produce for the patient? Perhaps you anticipate that the patient will receive $1x10^6$ cells per kilogram(kg) of body weight, but what is the concentration of cells? Can it be administered at $1x10^6$ per ml, or $1x10^7$ per ml? What effect does increasing the concentration have on the clumping or viability of the cells? If it is administered at $1x10^6$ cells per ml, then this equates to 70ml of product for a standard 70kg person, but you need to consider the doses for a wide range of patient weights (e.g. from 45 – 120kg). If you are looking at treating children, you will need to adjust for their smaller size, but it may not just be a case of reducing the volume, rather their different proportions (e.g. the head/brain of a newborn baby is proportionally much larger than that of an adult) may need you to make amendments to the dosing.

If it's a gene therapy, you may be administering locally, but then the volume that you can give will be lower. If it is an intrathecal injection, what is the volume you can give and can you get your product in the right concentration for this volume?

Finally, keep in mind that different routes of administration have different safety risk profiles and quality control requirements.

What is the shelf life of the product?

If you have any of your previous batches of your product in storage (fridge, freezer, liquid nitrogen) then running stability assays after defined periods of time will help to assess how long your product is stable at different temperatures. Equally, knowing the maximum time allowable after final formulation before drug administration will help the clinical trial team to manage their workflows. You may have only short-term storage data at the start of your trial, but it may be possible to extend the timeframes over time, as the stability data develops.

Regulatory

Regulatory obligations for new products are complex and each jurisdiction has its own processes. In Australia, the TGA regulates therapeutic goods (including medical devices), whilst the Office for the Gene Technology Regulator oversees any genetically modified products. As these are separate regulatory bodies, you may need to submit applications to both. The TGA has a wealth of information available, but also has a dedicated small and medium enterprise (SME) assistance site that will enable you to start a conversation with the TGA[3]. You should be starting to develop your regulatory considerations **very early** in your development plan. This is an area often overlooked during preclinical development but starting early will streamline your journey from research to clinical product.

What is your product?

The regulatory requirements are dependent on the type of product that you are developing. In general, gene therapies with *in vivo* genetic manipulation are classified as biological medicines and are managed through the Prescription Medicines Authorisation Branch of the TGA[4]. Cellular therapies are categorised

as biologicals. The type of manipulation will define the class of biological. For example, CAR-T therapies, which involve genetic manipulation *ex vivo* are class 4 biologicals, which also applies to products that contain live animal cells tissues or organs including pluripotent stem cells.

Is it gene modified and therefore needs OGTR application?

In Australia, the Office of the Gene Technology Regulator (OGTR) has oversight for all genetically modified organisms (GMOs). If your product will be manufactured in this country, then it is likely that you will need a licence from the OGTR. This is in addition to any approvals from the TGA. There are several classifications that cell and gene therapies fall under. Many of the CAR-T therapies final product may be classed as "exempt dealings" and don't require a licence, rather are managed through an institutional biosafety committee (IBC). You will need to supply evidence from preclinical work that satisfies the IBC that the exemption is justified. Any manufacture of vectors or viral transduction of cells will likely be classified as notifiable low risk dealing (NLRD) or a dealing not involving intentional release (DNIR). Your GMP manufacturing facility will have to be licenced by the OGTR. The classification of your final product will depend on the vector used. Information on the classification of contained dealings can be found on the OGTR website[5]

Are you applying for a CTN or CTA for approval for your clinical trial?

Australia has two pathways for authorising a clinical trial, a clinical trial notification (CTN) and a clinical trial approval (CTA). The choice of which scheme to use lies with the sponsor of the trial and the human research ethics committee (HREC), based on whether the HREC has appropriate scientific and technical expertise to be able to assess the safety of the product. If this is the case, they can approve a CTN, or recommend review under the CTA scheme. The CTN scheme can be used for earlier studies, but the CTA route is generally used for high risk or novel treatments (such as cell and gene therapies) and is mandatory for class 4 biologicals. However, if you already have approval for a trial for an equivalent indication from a comparable international regulator (e.g., US Food and Drug Administration, European Medicines Agency), then you may be able to file a CTN if you are simply importing the final product and not manufacturing locally. You can find more information on the CTN/CTA schemes in the TGA's clinical trial handbook[6].

Unlike other jurisdictions, there are no deadlines under which the TGA will review your CTA application. Additionally, if you are planning on treating patients in the US, then you will need to file an investigational new drug application (IND) to the FDA. It may therefore be worth considering filing the IND to the FDA and then submitting a CTN to the TGA if you are not changing your manufacturer.

Preclinical Data Package

All regulatory authorities will require a significant preclinical data package. This will include all the information on the mechanism of action (pharmacodynamics) and the parameters for manufacture described above as well as pharmacokinetics, biodistribution and toxicology. The TGA have issued a guidance on the required nonclinical studies[7] but it's important to note that this guidance is on top of the adopted European guidelines for nonclinical studies[8] with specific guidelines for gene therapies. The purpose of nonclinical studies for regulatory authorisation is to show you've considered the risks of the product to patients and that you have some indication of the likely efficacious dose range and toxicities that trial participants may experience. You should be discussing your preclinical package with the relevant regulatory authority as early as possible to ensure that you will have sufficient information for the regulators to make an informed decision on the risks associated with your product.

Clinical Trial

Before you submit any forms to the regulatory authorities, you will need to have considered your clinical trial and the manufacturing sites and processes as these will be required in your submission.

Who is running the trial?

Many clinical trials are run through a clinical research organisation (CRO), who can manage all aspects of the trial mentioned above. Your manufacturer may also be able to act as CRO or make suggestions.

Who are the physicians?

Working with clinicians at all stages of your research will focus your attention to the patient needs at an earlier stage of drug discovery. If you don't already have them in your research team, now is the time to include physicians. You will need treating physicians who will be able to advocate for your product in multidisciplinary team meetings. They will help identify potential trial participants. Many first-in-human studies will run out of one centre only but having a network of physicians who know about your trial and are excited about offering it to patients will improve recruitment.

Where will you recruit for the trial?

The recruitment centres for the trial will likely be dictated by the physicians that are involved, but it is worth considering where the trial will run and the logistics and supply chain of getting your product to the patients. This will be particularly relevant for autologous products where shelf life and the costs of shipping will need to be considered.

How many patients will you recruit?

Phase I trials are normally run as a dose escalation study, to determine optimal and safe dose for Phase II. If you're using a standard 3+3 design, then you are likely to need at least 12 patients. However, for rare diseases you may not have access to sufficient patients to be able to recruit even 12 patients, so you may need to consider alternatives. For your product to be commercially viable, it will need to be significantly better than the current standard of care. Therefore, it is important that you understand what the current standard of care treatment is and what it may be by the time you've completed all phases of clinical development. Based on the current treatments, you may need to consider whether to enrol specific groups of patients to maximise your chance of success. You may also need to consider inclusion/exclusion criteria for the trial to ensure a better chance of success. Your choice of collaborators or clinical research organisation will also play a big role in whether you are able to recruit the required patients in a suitable timeframe.

Protocol

The trial's primary and secondary endpoints are critical to determine the success of the trial. If the clinical endpoints are not well defined up-front then the trial can fail. At any phase of development, the outcome of a clinical trial can make or break a product. Whilst you may be assessing safety in Phase I, you should aim to capture as much data that can better inform your knowledge of the product for subsequent trials. For example, you may enrol patients with a specific disease, but by analysing in vivo expansion of cells or patient immune response profiles you are able to identify a subset of patients who are more likely to respond. Using this information will enable you to have different inclusion criteria for subsequent trials.

How much will it cost?

This is a very hard question to answer in a guidance document as costs are dependent on multiple factors. But running a clinical trial is expensive. Not only do you need to be able to manufacture sufficient product for the patients, but you will also need to consider costs for the management of patients whilst on trial, the number of pre-treatment and post-treatment tests, the data collection and analyses and management of all submissions to the TGA and HRECs. Remember that your manufacturer may not be the same as your CRO and so, the logistics of manufacture and patient care need to be matched up.

What will happen after Phase I?

It is important for you to think about what your plan is after Phase I – the reality of clinical trials is that they are very expensive to perform. Following Phase I, you will need to either raise significant capital to support moving into Phase II studies or consider licencing/selling to a larger pharma/biotech company. Both of these approaches will need for you to have a good value proposition and solid data package, so you will need to plan your Phase I for maximum potential. This is not the time to be cutting corners, it will

devalue your product (if the investors can't see a path for approval) or require you to perform more / or refined scope of Phase I trials (if you have to change your product or process significantly).

It is worth considering your plans for Phase II even before you start your Phase I trial, as this will help you to develop your longer-term strategy. In Australia, initial experimental studies in human volunteers don't require a GMP manufacturing licence from the TGA. However, there is an expectation that investigational products are manufactured in accordance with any applicable GMP. According to the TGA, "initial experimental studies in human volunteers means first-in-human trials, and manufacture of all other investigational medicinal products are subject to inspection and licencing"[9]. Importantly, the GMP exemption does not refer to all Phase I trials. All subsequent trials will need the product to be manufactured in a facility with manufacturing licence from the TGA. So, plan for Phase II when doing your tech transfer to the manufacturing partner. Many investigator-initiated Phase I trials do not progress further than Phase I. The academics and physicians involved are interested in treating their patients, but do not have a commercial endpoint in mind. Because of this, Informa, one of the leading providers of clinical and competitor insights, does not include the investigator-initiated trials (IIT) in their statistics of likelihood for approval. Having a clearly defined path to Phase II and beyond will make your product a better investment proposition. You will be able to progress quicker, meaning that more patients are treated with your product and ultimately closer to realising a meaningful change to current treatment options.

Whilst it is important to plan for success, it is also worth having an alternative approach for if your trial fails. The chances that your product will go all the way to approval are quite slim. A recent report has the likelihood for approval of a product in Phase I at 7.9%; for CAR-T's this is 17.3% and gene therapies, 10% (ref [10]). So, what is your back up plan?

How long will it take to be able to start the clinical trial?

The earlier you reach out to the manufacturing facilities and CROs the better. In particular, the clean rooms for manufacture are in high demand, and if the facilities know you are getting ready then they will be able to manage workflows to include your project. They will also highlight any areas of product development that are needed prior to the tech transfer. Here in Australia, many of the manufacturing facilities are located in a hospital or an academic setting, which means that they have better access to patients, and the structures around clinical trials. Getting the manufacturing process established and clean room space/time allocated will likely be one of the gating factors for clinical trial readiness. Submission of the documentation to the regulatory authorities also takes time to process and this is likely another key factor in when your trial will start. There is also a significant shortage of plasmid DNA and vector supply worldwide, with reports of more than one year lead time on these, so it is vital that you engage a supplier early in the tech transfer.

Summary

Translation of your lab-based research to clinical manufacture will require a shift in mindset from research to reproducibility. Tech transfer and process development will take time and coordinated efforts from both you and your manufacturing partner, however this is not the time to be cutting corners or going for the quick fix. Focusing on the quality of your manufacturing processes even before Phase I will improve your chance of success in further/future studies. **Early conversations with manufacturing partners, CROs and the regulators will assist you in streamlining your preclinical processes**.

The TIA Mission

Therapeutic Innovation Australia's (TIA) Cell and Gene Therapies 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 research community. The capability is a consortium of five public-sector GMP facilities for cell and gene therapies. **Early engagement with TIA or one of the facilities will enable you to leverage their**

significant expertise and expedite your translation to clinical development.

Acknowledgements

Thank you to all the TIA-supported facilities for their input into this document. In particular, Sharon Sagnella (Cell & Molecular Therapies), Jennifer Hollands (Cell Therapies Pty Ltd.), Zlatibor Velikovic (Cell and Tissue Therapies WA), Leon Scott (previously of Q-Gen) and Margot Latham (Sydney Cell and Gene Therapy). All provided valuable insights, based on their interactions with early translational researchers. Thanks also to Helen Wray for her thoughts on translating therapies to the clinic.

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

---

[1] Crossing the Valley of Death – Guidance for Researchers Translating a Research Discovery into and Advanced Therapeutic Product. Therapeutic Innovation Australia, 2021. https://www.therapeuticinnovation.com.au/_files/ugd/4db921_e063b07b241c4e30aea26e8add087293.pdf
[2] Australia's Regenerative Medicine Manufacturing Capacity and Capability, 2021. https://www.ausbiotech.org/documents/item/666
[3] Therapeutic Goods Administration, SME Assist https://www.tga.gov.au/sme-assist
[4] Australian Regulatory Guidelines for biologicals, https://www.tga.gov.au/classification-biologicals
[5] Guidance on the classification of contained dealings with viral vectors, September 2012. https://www.ogtr.gov.au/resources/publications/guidance-classification-contained-dealings-viral-vectors
[6] Australian Clinical Trial Handbook, Version 2.4, August 2021. https://www.tga.gov.au/resource/australian-clinical-trial-handbook
[7] Guidance 23: Nonclinical Studies, TGA, September 2014. https://www.tga.gov.au/guidance-23-nonclinical-studies
[8] Non-clinical Guidelines, European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/non-clinical-guidelines
[9] Australian Clinical Trial Handbook, Version 2.4, August 2021 https://www.tga.gov.au/resource/australian-clinical-trial-handbook
[10] Clinical Development Success Rates and Contributing Factors 2011-2020, February 2021. https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2021/files/reports/2021-clinical-development-success-rates-2011-2020-v17.pdf.