The future of phage clinical trials in Australia

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Australia is well positioned to conduct clinical trials in phage-based technology. Despite challenges with translating phage therapy to mainstream medicine, our regulations are designed for safe and innovative development. Recent success indicates that Australia is ideal for conducting further phage clinical trials. There are also expert clinical research organisations and generous tax incentives.

Historically, there have been barriers to translating phage therapy from 'bench to bedside'. Some strategies for broader acceptance of phage therapy have been evaluated[1–3] and the industry consensus is to gather quality clinical evidence regarding safety, tolerability, and efficacy[2]. As such, clinical trials (CTs) are a critical interface for translating phage therapy. The components that can influence the success of a clinical trial are depicted in Figure 1.

More broadly, the translation of phage therapy can be broken down into three main components: the phage, the CT design, and the regulations. There is ongoing debate regarding the ideal strategy for translating phage technologies. Some researchers suggest that instead of using natural phage cocktails (a mixture of numerous strains of phage targeting the same host bacterium), phage-based products such as lysins and depolymerases may be used as an alternative (and simpler) pathway to regulatory compliance[4,5], while other researchers argue that, in fact, regulations should change[5,6]. Instead, the author proposes that the main solution to translating phage therapy is to change the CT design. This article summarises: some phage technologies; recent phage CT outcomes, the potential design for other phage-related CTs; and the process of conducting a phage CT in Australia.

Phage cocktails

Phage cocktails, rather than individual isolates, are often used to treat recalcitrant biofilms rather than individual isolates because they broaden the range of susceptible hosts and reduce the risk of replacing treated hosts with phage-resistant mutants[7,8].

However, phage cocktails often raise more regulatory flags. Phage replication can result in mutant phages and there are concerns regarding potential genetic transfer of pathogenic elements, such as shiga toxin to bacteria. High-throughput sequencing may be an effective tool used during a CT to collect phage genetic data[9] and enable monitoring of mutations while informing clinical researchers and regulators. In addition, this may assist with collecting pharmacokinetic and dose finding data[10]. Others suggest that genetically modified phages (GM-phages) may control for random genetic transfers and mutations, thus improving the chances of regulatory success.

Genetically modified phage

Over the past 30 years, phages have proven to be genetically-malleable tools[11–15]. New developments using genetic engineering (a.k.a. synthetic biology) to create phages[12] may be relevant to the future of phage CTs. Some researchers compare GM-phages to genetically-programmable machines[16] and, if gene switches are inserted, they may also reduce risks associated with uncontrolled gene transfer[15]. In 2018, the Nobel Prize in Chemistry for was awarded to three scientists for their work in 'phage display of peptides and antibodies'[17,18] and 'directed evolution'[19]. Some researchers argue that genetic engineering of phages may secure intellectual property and in doing so increase the potential for funding CTs. Moreover, since the discovery of CRISPR/Cas9 there has been a rapid increase in the number of technologies using GM-phages[20]. Functions including conditional expression, conditional replication, and non-integration can be included. Although it is yet to be demonstrated, such innovation may improve the chances of regulatory approval while also providing an opportunity to create new industry for Australia.

Phage clinical trials

In the recent past, many phage therapy CTs have used traditional fixed designs and methods that have not been able to adapt their trial parameters to improve scientific precision and provide groundwork for subsequent trials. In 2009, results from a British phase I/II CT demonstrated efficacy using a single dose of a topical

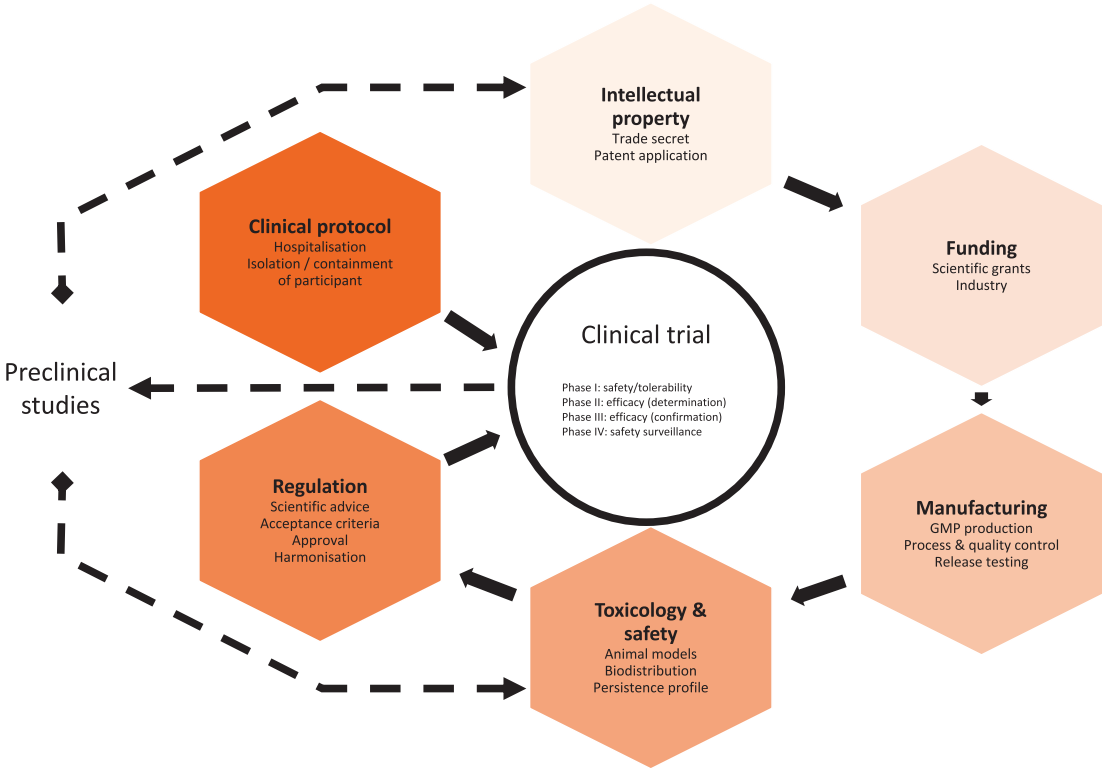

Figure 1. Essential steps in the translation of viruses in the clinics[8].

six-phage cocktail for antibiotic-resistant *Pseudomonas aeruginosa* in patients with chronic otitis. Unfortunately, many of the patients had recurrence of their infection. The authors recommended another randomised, double-blind CT with multiple doses but this trial never occurred[21].

In 2017, researchers from The University of Adelaide presented promising results from a landmark phase I CT evaluating the safety and tolerability of an intranasal irrigation containing a three-phage cocktail[22] targeting *Staphylococcus aureus* in patients with surgically-recalcitrant chronic rhinosinusitis[23]. Safety, tolerability, and efficacy were demonstrated, and like the otitis trial, future recommendations included longer duration of the phage therapy.

In 2019, results from the European PhagoBurn CT were published. This was the world's first phage CT to be performed according to Good Manufacturing Practice and Good Clinical Practice. This multi-centre, randomised, controlled, double-blind phase I/II CT demonstrated tolerability of a 12-phage cocktail targeting *Pseudomonas aeruginosa* burn wound infections but was unable to demonstrate efficacy. Participant recruitment was slower than expected because many of the screened participants had polymicrobial infections. In addition, the bacteria isolated from participants who failed phage therapy were resistant to low phage doses. Therefore, the authors recommended increased phage dose in future to demonstrate efficacy without allowing the opportunity for phage-resistant mutants to develop[24].

Adaptive design

Adaptive CT design[25] may have advantages over the aforementioned traditional fixed randomised, controlled design for further development of phage technologies. Adaptive CT designs are less rigid and allow for adjustment of components such as dose, frequency, duration, allocation to different treatment arms, and sample size during the CT. The statistical modelling for adaptive CTs generally use a Bayesian inference continuous reassessment approach[26], which can create updated distributions as the number of participants increases. In doing so, valid real-time data can be obtained from the smallest possible sample size without exposing participants to unnecessary risks. One drawback of this approach is that preparation of an efficient adaptive CT design may require multidisciplinary input and the use of simulation software[27]. Whilst this would increase lead-up costs, it often results in overall cost reduction and is an effective approach to flagging trial related issues in advance. Ultimately, adaptive designs can evolve to suit the dynamic nature of phage therapy CTs. They may also be useful in evaluating other GM-phage applications such as anticancer and gene-based therapy phage products.

Regulatory process in Australia

In Australia, the Therapeutic Goods Administration (TGA) has adopted many of the European Medicines Agency policies. Both natural phage and GM-phage are considered 'gene transfer

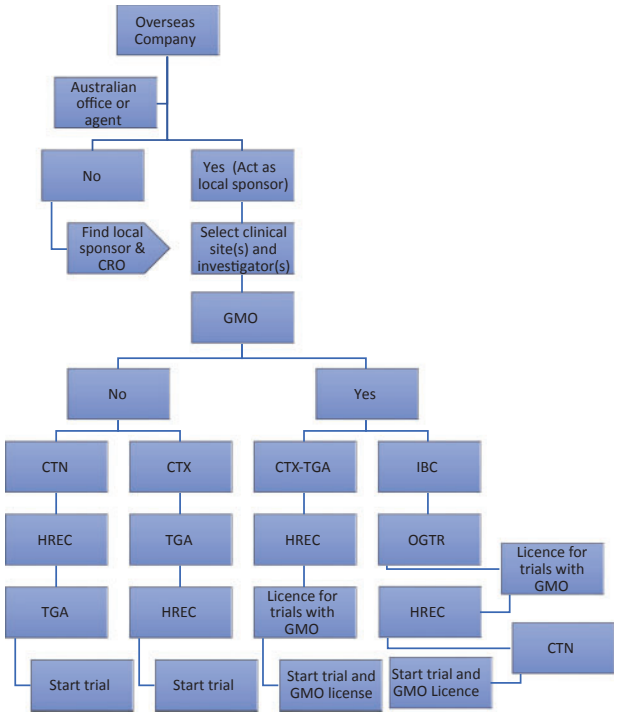

Figure 2. How to start a clinical trial in Australia for unregistered products. Adapted from LSQ (2016) Starting a Clinical Trial[12]. CRO, Contract Research Organisation; GMO, Genetically modified organism; CTN, Clinical Trial Notification; CTX, Clinical Trial Exemption; IBC, Institutional Biosafety Committee; HREC, Human Research Ethics Committee; TGA, Therapeutic Goods Administration; OGTR, Office of the Gene Technology Regulator.

biological medicines'. The Australian regulatory process for both natural and GM-phage is shown in Figure 2[28].

There are currently no Australian-owned phage therapy companies. For CT to be undertaken in Australia, the law mandates that an overseas company must have a local representative, also known as a sponsor (a person or entity who resides in Australian and either imports, exports, or manufactures therapeutic goods). The person or entity who is in this role has primary responsibility for many of the decisions made during the planning and execution of the CT. The local sponsor will then review and select the appropriate clinical site(s) and investigator(s). The subsequent regulatory pathway will then depend on whether the phage is genetically modified. The sponsor can confirm this based on the Gene Technology Act[29] and the Gene Technology Regulations[30].

If the phage (product) is not a result of genetic modification, the sponsor will then decide whether it should pursue the TGA's Clinical Trial Notification (CTN) scheme or the Clinical Trial Exemption (CTX) scheme. This should be done in collaboration with the Human Research Ethics Committee (HREC) and will depend on whether the HREC has appropriate scientific and technical expertise to assess the safety and efficacy of the product. The CTN scheme is often viewed as efficient and cost-effective compared to the comprehensive review required via the CTX pathway. However, one benefit of the CTX pathway is that once a CTX application is approved, the sponsor may conduct any number of CTs under that application without further assessment by the TGA. For any CT, a HREC evaluates whether the risk-benefit ratio is favourable for the participant. To improve the potential benefits to the participant, the product should target a disease of unmet need and have demonstrated safety and efficacy in preclinical studies. In order to make a reasonable assessment, the HREC evaluates at least three essential documents: investigator brochure, trial protocol, and patient informed consent form. The investigator brochure should include both phage-relevant data[8] and published studies that support validity (e.g. randomisation, sample size calculation, and blinded outcome assessments[31,32]).

Should the product be a genetically modified organism (GMO), then an alternative pathway will be required. A GMO must first be evaluated by an approved Institutional Biosafety Committee (IBC) which will determine the risk of GMO release into the environment and the suitability of the licence applicant to be accredited under the Gene Technology Act. Although this is an additional requirement, Australia's regulators do not duplicate evaluations and the National Gene Technology Scheme[33] ensures safety without stifling innovation[33].

Once the Office of The Gene Technology Regulator issues a licence to the sponsor, the IBC and HREC will recommend either the CTX or CTN scheme to the TGA. This is different to the natural phage pathway and serves to eliminate regulatory duplication. Additionally, if the product is manufactured overseas, an import permit from the Department of Agriculture and Water Resources may be required. This can be evaluated through the Biosecurity Import Conditions website tool[34]. Participant recruitment can then commence once all appropriate approvals are obtained.

Why Australia?

Australia is considered attractive to international sponsors wishing to conduct CTs because of key financial and logistical frameworks. The research and development tax incentive scheme provides up to 43.5% reduction in a company's income tax liability and given that the average phase I CT costs greater than $2m, the potential savings are significant. In 2013, Australia setup The National Mutual Acceptance Scheme, which is a Memorandum of Understanding between most states and territories to allow for 'once only' scientific and ethical review for multi-centre CTs conducted at public health organisations. This improves efficiency by reducing duplication. Readers can review the numerous clinical trial documents that the Australian government has provided online[35–37].

The translation of phage therapy requires an adaptive approach. Out of the three components, CT design is easier to adjust than the

phage, and much easier than the regulations. For the phage-therapy industry to reposition itself from 'controversial' and 'fringe' to mainstream, judicious use of resources in high yield trials that adapt to confounding factors should be prioritised. Nonetheless, with collaboration and experienced investigators, these hurdles can be minimised and Australia can establish itself as a good choice for phage CTs due to high quality infrastructure, efficient regulators, and the research and development tax incentive.

Conflicts of interest

The author declares no conflicts of interest.

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Biography

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