Environmental Protection Authority
Te Mana Rauhī Taiao

New Zealand Government

MEMORANDUM

Supporting information for the consideration of APP204075

To:	Siobhan Quayle, Group General Manager, Regulatory Systems and Operations
From:	Dr Tim Strabala, Acting Manager and Principal Scientist, New Organisms
Date:	19 August 2020
Subject:	Supporting information for the consideration of application APP204075

Purpose

1. This memo provides information to support your consideration of Application APP204075. This memo is intended to be read in conjunction with the draft decision.

The application and information for consideration

2. Application APP204075 from The Malaghan Institute of Medical Research ('the applicant') proposes to develop genetically modified human cells for the packaging of 3rd generation self-inactivating lentiviral vectors as discussed in the application, and the subsequent use of these vectors to genetically modify both human leukaemia (a type of white blood cell cancer) cells and T cells (a type of white blood cell involved in the human immune response) with immune-modulating chimaeric antigen receptor molecules (please see the application for more information). The applicant sees this as a continuation in their development of new therapies for blood cancers, as a supplementary application to their existing approval APP203214, similar to those that are currently being developed and tested by the applicant.

3. The current application under consideration here is essentially identical to that of APP203214, which was also submitted by the applicant, and which was subsequently approved by the Chief Executive of the EPA in 2017, as per the delegations that existed at that time. Human T cells developed under APP203214 were subsequently approved for conditional release under APP203750 in 2019, for the Malaghan Institute's ongoing Chimaeric Antigen Receptor-T cell (CAR-T cell) clinical trial. The current application is solely to expand the range of T cells that are approved for development from CD8-positive (CD8+) T cells (CD8 is a cell surface protein that is used in cell sorting machines to select specific cell types out of a mixture of cell types, in this case, human blood cells), to all human T cells.

4. The broadening of the approval to allow the development of all human T cell types in the current application, beyond those that are already approved under APP203214 might under other circumstances be viewed as a 'minor in effect' change, and thus eligible for an amendment of the approval under section 67A of the HSNO Act. However, in this instance, the decision in

APP203214 is specific for CD8+ T cells, and decisions are not amendable. Thus, a new application was required as more has been learned about CAR-T cells in this and other research.

5. The T cells developed under this application, should it be approved, may be released under the applicant's existing release approval of a qualifying medicine under section 38I of the Hazardous Substances and New Organisms Act 1996 (the HSNO Act), APP203750.

6. This is a Genetic Modification Development in containment Rapid assessment of projects for low-risk genetic modification considered under s42A of the HSNO Act and the HSNO Low-Risk Genetic Modification Regulations 2003.

7. The application was formally received on 7 August 2020.

Host organisms, and ethical and Māori considerations

8. As in the applicant's current approval APP203214, the human cell lines named are all well-characterised lines used in this type of work. In particular, HEK 293T cells are commonly used for the creation of lentiviral vectors and contain the necessary viral genes needed to package the CAR gene into a viral coat on separate plasmids (see Fig. 1 of the application) to minimise the risk of creating a replication-competent retrovirus. Four independent recombination events would be required for this to happen, and the likelihood of homologous recombination (DNA strands rejoining using cellular mechanisms to repair natural DNA strand breaks using sequence similarity via base-pairing) is very low without homologous sequences among the plasmids in the cells to enable this.

9. Because the replication-defective packaged vectors proposed for use in this application – should it be approved – lack the key viral *gag, pol,* and *env* genes necessary for the replication of lentiviruses and other retroviruses, they are not considered to be organisms, per statutory determination decision APP202444. Thus, the only organisms proposed for development in this application are the human packaging, leukaemia, and primary T cell lines.

10. The applicant proposes to use the packaged vectors to transduce a human leukaemia cell line, to test the vector titre (the number of transducing particles per unit volume). The primary CD3+ T cell lines to be genetically modified into CAR-T cells will come from the cancer patients in the study that the applicant is currently conducting at Wellington Hospital. After these cells are genetically modified, they will be returned to the same cancer patients from whom they were removed, under the conditional release approval APP203750. As stated in the application, relevant ethical approvals and Māori consultation and informed consent procedures will be carried out and obtained through hospital ethics committees.

11. Kaupapa Kura Taiao stated that "…the CAR-T cells to be developed in this application, should it be approved, are intended for release under the existing approval APP203750, for the clinical trial for the treatment of certain blood cancers. This approval received a full Māori Perspectives Report from Kaupapa Kura Taiao at that time. I understand that the changes proposed by this application are minor and that the impact for the activities covered by this application and APP203750, from a Māori perspective, is negligible."

Comments from external agencies

12. The Department of Conservation (DOC) and the Ministry for Primary Industries (MPI) were each provided with a copy of the application and given the opportunity to comment. DOC indicated that they consider the importation into containment or development in containment of low-risk GMOs

to carry very low risks to biodiversity, and they are therefore not opposed to the approval of this application. MPI did not return comment on the application.

The draft decision

13. We evaluated the risks associated with this application as being low, and considered the risk assessment of these development activities to be straightforward. However, this application pertains to the development of human T cells that will be released as a qualifying medicine under s38I of the HSNO Act (Approval APP203750, as discussed above), if the current application is approved. We therefore elected to prepare this memo to accompany the draft decision for this application to support your consideration, in place of the usual "Key points" document normally provided with low-risk rapid applications.
14. Given that the applicant already holds a nearly identical approval (APP203214) to the one sought in this application, we believe that the applicant's current experience with their containment regime (including that the Facility is approved to the PC2 standard by MPI) is sufficient to contain the genetically modified cell lines specified in this application.

Proposed controls

15. The proposed controls are set out in Table 2 of the draft decision and Table 2 of the draft approval. The proposed controls are consistent with the MPI/EPA laboratory containment standards in addition to the AS/NZS 2243.3 (2002) containment standards as required in the Low-Risk regulations. These controls thus prescribe a set method by which the outcome must be achieved, because this is specified in the standards.
16. Based on the information provided in the application, this memorandum, and the draft decision, we recommend that you approve application APP204075 under sections 40(1) and 42A of the HSNO Act.

19 August 2020

Dr Tim Strabala **Date**
Acting Manager and Principal Scientist
New Organisms