Environmental Protection Authority
Te Mana Rauhī Taiao

New Zealand Government

MEMORANDUM

Application	APP204075
Applicant	The Malaghan Institute for Medical Research
From	Dr Tim Strabala, Acting Manager and Principal Scientist, New Organisms
To	Dr Clark Ehlers, Acting General Manager, Hazardous Substances and New Organisms
Purpose of the Memorandum	Section 42A Pathway assessment for APP204075
Date of Advice	24 July 2020

Purpose

1. This memo provides my pathway assessment and recommendation for your consideration of application APP204075 to develop genetically modify human cell lines that package 3rd generation self-inactivating lentiviral vector particles, and to generate genetically modified human T cells expressing genes that regulate the activity of human immune cells, using the aforementioned lentiviral vectors.

2. At this stage, no application has been formally submitted, pending your decision on the application pathway.

Background

3. Application APP204075, from the Malaghan Institute of Medical research (the applicant), intends to seek approval to develop genetically modify human cell lines that package 3rd generation self-inactivating lentiviral vector particles, and to generate genetically modified human T cells expressing genes that regulate the activity of human immune cells, using the aforementioned lentiviral vectors. It is intended that the application will be submitted under sections 40(1) and 42A of the Hazardous Substances and New Organisms (HSNO) Act 1996 ('the HSNO Act').

Statutory criteria for pathway assessment – s42A

4. Under section 42A of the HSNO Act, an application made under section 40(1) to develop a new organism may, instead of specifying the information required by or under section 40(2), describe:

   (a) a project for the development of genetically modified organisms; and

   (b) the identity of the host organisms; and

   (c) the nature and range of the proposed genetic modifications.

5. If an application provides all of the above information, the EPA may decide to undertake a rapid assessment of the adverse effects of carrying out the project if it is satisfied that:

   (a) any host organism specified for the project meets the criteria for host organisms prescribed in the Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 2003 (Low-Risk Regulations) (i.e. are either **"category 1 host organisms"** or **"category 2 host organisms"**); and

   (b) any genetic modification specified for the project meets the criteria for genetic modification procedures prescribed in the Low-Risk Regulations (i.e. are either **"category A genetic modifications"** or **"category B genetic modifications"**).

6. The decision to undertake a rapid assessment under section 42A of the HSNO Act is currently sub-delegated to the Manager, New Organisms, by the Chief Executive[1] under the instrument of delegation effective as of 6 March 2020. However, as I am currently the Acting Manager, New Organisms, but I am conducting this assessment under my usual role of Principal Scientist, New Organisms, the decision must be undertaken by the General Manager of Hazardous Substances and New Organisms.

Assessment of the application against statutory criteria

7. I have assessed the application against the statutory criteria and my findings are set out in the table below.

Checklist	Yes	No	Details
Information Requirements (s 42A(1))			
Does the application describe a project for the development of genetically modified organisms?	☒	☐	*To develop genetically modify human cell lines that package 3rd generation self-inactivating lentiviral vector particles, and to generate genetically modified human T cells expressing*

[1] Per the sub-delegation dated 6 March 2020 from the Chief Executive to the Manager, New Organisms, under delegated authority dated 6 May 2016 from the EPA to the Chief Executive pursuant to section 19 of the Act.

Checklist	Yes	No	Details
			genes that regulate the activity of human immune cells, using the aforementioned lentiviral vectors.
Does the application describe the identity of the host organisms?	☒	☐	*Human (*Homo sapiens*) cell lines(See Schedule)*
Does the application describe the nature and range of the proposed genetic modifications?	☒	☐	*Packaging of 3rd generation self-inactivating lentiviral vector particles in human cell lines, and generation of genetically modified human T cells expressing genes that regulate the activity of human immune cells, using the aforementioned lentiviral vectors.*
Host Organisms (s 42A(2)(a) & regs 6 & 7)			
Are the host organisms clearly identifiable and classifiable according to genus, species, and strain or other sub-specific category as appropriate?	☒	☐	*Human (*Homo sapiens*) cell lines (See Schedule)*
Category 1 host organisms Do the host organisms satisfy all of the following: (a) are not normally able to (or contain infectious agents normally able to) cause disease in humans, animals, plants, or fungi; (b) do not produce desiccation-resistant structures, such as spores or cysts, that can normally be disseminated in the air; (c) are characterised to the extent that their main biological characteristics are known; and (d) do not normally infect, colonise, or establish in humans.	☒ ☒ ☒ ☒	☐ ☐ ☐ ☐	

Checklist	Yes	No	Details
Category 2 host organisms Are the host organisms either: (a) micro-organisms of risk group 1[2] or risk group 2[3] that either: (i) are or contain an infectious agent pathogenic to humans, animals, plants, or fungi; or	☐	☐	
(ii) produce desiccation-resistant structures, such as spores or cysts, that may normally be disseminated in the air; or	☐	☐	
(iii) are not characterised to the extent that its main biological characteristics are known; or	☐	☐	
(iv) normally infect, colonise, or establish in humans;	☐	☐	
(b) a mammalian cell line containing active viruses or infectious agents normally able to cause disease in humans;	☐	☐	
(c) a whole animal, vertebrate or invertebrate, including oocytes, zygotes, early embryos, and other cells able to grow without human intervention into a whole animal; or	☐	☐	
(d) a whole plant either: (i) with a reproductive structure and that is not kept in a closed container; or	☐	☐	
(ii) with a reproductive structure and that is kept in a closed container; or	☐	☐	
(iii) without a reproductive structure and that is not kept in a closed container.	☐	☐	

[2] Risk group 1 means micro-organisms that are unlikely to cause diseases in humans, animals, plants, or fungi.

[3] Risk group 2 means micro-organism that: (a) may cause disease in humans, animals, plants, or fungi but are unlikely to be a serious hazard to laboratory personnel, the community, animals, or the environment; and (b) have effective treatment and preventive measures with respect to any infections that they may cause; and (c) present a limited risk of the spread of infection.

Checklist	Yes	No	Details
Proposed genetic modifications (s42A(2(b) & regs 4 & 5)			
Do the proposed genetic modifications involve any of the developments specified in the Schedule to the Low-Risk Regulations (being developments that are considered not to be low-risk modifications)?	☐	☒	
Category A genetic modification			
Do the proposed genetic modifications satisfy all of the following:			
(a) involve a category 1 host organism;	☐	☐	
(b) carried out under a minimum of PC1 containment[4];	☐	☐	
(c) do not increase the pathogenicity, virulence, or infectivity of the host organism to laboratory personnel, the community, or the environment; and	☐	☐	
(d) do not result in the genetically modified organism having a greater ability to escape from containment than the unmodified host organism.	☐	☐	

[4] PC1 containment means (a) the conditions for the physical containment of organisms described as Physical Containment Level 1 (PC1) in AS/NZ containment standard 2243.3:2002 (Safety in Laboratories Part 3: Microbiological Aspects and Containment Facilities); and (b) the modifications referred to in the following MAF Biosecurity Authority containment standards: (i)154.03.02 (31 October 2002) (containment facilities for micro-organisms): (ii) 154.03.03 (31 October 2002) (containment facilities for vertebrate laboratory animals): (iii) 154.02.08 (31 October 2002) (transitional and containment facilities for invertebrates): (iv) 155.04.09 (24 March 2003) (containment facilities for new organisms, including genetically modified organisms, of plant species).

Category B genetic modification Do the proposed genetic modifications satisfy the following:		
(a) carried out under a minimum of PC2 containment[5]; and either	☒	☐
(b) if a category 1 host organism is used both of the following are satisfied:		
(i) the nucleic acid that is introduced is be characterised to the extent that either;		
(A) its sequence is known; or	☒	☐
(B) its gene function is understood; and	☒	☐
(ii) the modification does not result in either of the following:		
(A) a genetically modified organism that is more pathogenic, virulent, or infectious to laboratory personnel, the community, or the environment than a category 2 host organism; and	☐	☒
(B) the genetically modified organism having a greater ability to escape from containment than the unmodified host organism.	☐	☒
(c) if a category 2 host organism is used both of the following criteria are met:		
(i) the modification involves either:		
(A) a host organism that is not normally able to cause disease in humans, animals, plants, or fungi; or	☐	☐
(B) a host organism that is normally able to cause disease in humans, animals, plants, or fungi provided that the nucleic	☐	☐

[5] PC2 containment means (a) the conditions for the physical containment of organisms described as Physical Containment Level 2 (PC2) in AS/NZ containment standard 2243.3:2002 (Safety in Laboratories Part 3: Microbiological Aspects and Containment Facilities); and (b) the modifications referred to in the following MAF Biosecurity Authority containment standards: (i)154.03.02 (31 October 2002) (containment facilities for micro-organisms): (ii) 154.03.03 (31 October 2002) (containment facilities for vertebrate laboratory animals): (iii) 154.02.08 (31 October 2002) (transitional and containment facilities for invertebrates): (iv) 155.04.09 (24 March 2003) (containment facilities for new organisms, including genetically modified organisms, of plant species).

	acid that is introduced is characterised to the extent that satisfies <u>all</u> of the following:		
	1. its sequence is known;	☐	☐
	2. its gene function is known; and	☐	☐
	3. its potential gene products are understood; and	☐	☐
(ii)	the modification <u>does not either</u>:		
	(C) increase the pathogenicity, virulence, or infectivity of the host organism to laboratory personnel, the community, or the environment; and	☐	☐
	(D) result in the genetically modified organism having a greater ability to escape from containment than the unmodified host organism.	☐	☐

8. In summary, I have concluded that the information requirements in section 42A(1) are satisfied and the host organisms and proposed genetic modifications conform to the requirements for host organism and genetic modification in the Low-Risk Regulations as required by section 42A(2).

Other Considerations

9. The decision to carry out a rapid assessment under section 42A is a discretionary decision. Therefore, you are not obliged to carry out a rapid assessment just because the criteria in section 42A are met. In deciding whether to carry out a rapid assessment of the application, you should be aware of the following:

   - The applicant already holds an approval for the development of lentiviral vectors and the development of genetically modified T cells, which is limited in its purpose solely to CD8+ T cells. The current application broadens the approved T cells beyond the $CD8^+$ T cells allowed under their current approval to all human T cells.

Recommendation

10. I have assessed the application against the statutory criteria and consider that it meets the requirements set out in section 42A of the Act, and the Low-Risk Regulations.

11. I therefore recommend that a rapid assessment of this application is undertaken in accordance with section 42A of the HSNO Act.

24 July 2020

Dr Tim Strabala Date

Acting Manager and Principal Scientist, New Organisms

Decision

Rapid assessment critera

☒ I agree that application APP204075 meets the requirements of section 42A of the HSNO Act.

☐ I do not agree that application APP204075 meets the requirements of section 42A of the HSNO Act.

Decision whether to undertake rapid assessment

☒ I have decided that application APP204075 should be subject to a rapid assessment of the adverse effects of carrying out this project under section 42A of the HSNO Act.

☐ I have decided that application APP204075 should not be subject to a rapid assessment of the adverse effects of carrying out this project under section 42A of the HSNO Act.

Environmental Protection Authority
Te Mana Rauhī Taiao

Dr Clark Ehlers Date 27/07/2020

General Manager (Acting), Hazardous Substances and New Organisms

Schedule: List of organisms, risk categorisations and genetic modifications proposed for development under APP204075

Organism	Taxonomic name	Organism and genetic modification risk categorisations
Human viral vector packaging cell lines and human cancer patient-derived primary T cell lines	*Homo sapiens*	Category 1 host organism Category B genetic modification