Loughborough University

Health & Safety Unit Use Only	
Ref No:	
Department Use Only	
Ref No:	CBE 158

RISK ASSESSMENT of WORK with

GENETICALLY MODIFIED ORGANISMS

The requirements of Genetically Modified Organisms (Contained Use) Regulations 2000 are reflected in the University Health and Safety Policy which requires that risk assessment of all work with Genetically Modified Organisms ***must*** *be carried out in advance of work commencing and, in addition,* ***must be scrutinised and approved*** *by the University's relevant Safety personnel. The tables at the end of this document are drawn from the current legislation and the appropriate table* ***must*** *be completed as part of the assessment. Finally,* ***WORK MUST NOT BEGIN*** *until the proposal has been* ***approved*** *and clearance has been given via Health and Safety.*

Date submitted	21/11/2017	**Date approved**	

Please provide the following general information:

School/Department	Centre for Biological Engineering, Chemical Engineering, AACME

Principal investigator	Dr Elizabeth Ratcliffe	**Position**	Vice-Chancellor's Lecturer in Biological Engineering, Programme Director for Bioengineering
E-mail address	E.Ratcliffe@lboro.ac.uk	**Phone no.**	01509 227590

Please give a brief and descriptive title for this risk assessment

Title	PEI Transfection of HEK293 / HEK293T cells for improved vector uptake for gene therapy production

Please provide a brief description of the nature of the work, identifying any GMMs produced *(e.g. virus vector with insert)*, and their use to transform cells. Please identify the components of the project for which this risk assessment is carried out.

This risk assessment is for a research project that aims to improve the manufacturing process of gene therapies, specifically the transfection of HEK293 /or HEK293T cells with a vector. The research will be performed at Contaminant Level 2 standards, with a view towards subsequent research at GMP standards.

This risk assessment is for the research to be conducted within the CL2 laboratory where the operators will undertake a polyethylenimine transfection of a human embryonic kidney cell line (HEK293/ HEK293T) with a pDG helper and packaging plasmid / vector and a RK-hAILP1 plasmid.

Donor	Human
Name of gene/nucleic acid sequences	AILP1 gene More info can be found on: https://www.ncbi.nlm.nih.gov/gene/23746
Vector	RK-hAILP1 with pDG helper plasmid
Host	HEK293 / HEK293T
ACDP category* of host (where appropriate)	N/A

*The ACDP categorisation of biological agents can be found in the *Approved List of Biological Agents* published by the Health and Safety Executive.

Note: The questions in this proforma are designed to ensure that all the relevant issues have been addressed for the majority of Risk Assessments for work involving Genetic Modification at the University of Loughborough. However in the interests of streamlining the majority of applications, and because not all possible applications of genetic modification may have been anticipated, there may be instances in which answer of these questions alone may not be sufficient for a full risk assessment. The Genetic Modification Safety Committees reserve the right to request additional information. For a more complete description of the requirements of a Risk Assessment, refer to ACGM notes and newsletters, and the Guidelines to the 2000 Regulations. Less detail will be required for commonly used and familiar host/vector systems than for those less widely known or characterised. References may be helpful in some instances.

It may be appropriate to write the assessment to cover a range of closely related GMOs, e.g. a defined family of genes, a range of vectors with similar properties, complete and partial sequences, with and without expression; however the assessment and containment conditions proposed must reflect the greatest potential hazard of any of the range of GMMs covered by the assessment.

Do not feel constrained by the box sizes, in some cases considerably greater amounts of information may be required. The box sizes should expand to accommodate your text. To add further rows to a table, use tab key when cursor is in the last box.

Any potentially confidential information should be highlighted, e.g. by use of **red text**. This will include all personal information, and possibly e.g. commercially sensitive information, which the applicant wishes **NOT TO APPEAR ON THE PUBLIC REGISTER**. NB There are tight restrictions on what will be accepted as confidential. The remainder of the risk assessment must be understandable without the confidential information.

It may be possible for outside bodies to access information in this form under the Freedom of Information Act, unless it can be categorised as an exemption. Furthermore, work with organisms listed in Schedule 5 of the Anti-terrorism, Crime and Security Act 2001, or genetic material from those organisms, may be notifiable to the Home Office.

Characteristics of the Donor, Insert, Vector and Host

Name (species/strain if appropriate) **and characteristics of the source of the nucleic acid sequences ("the donor)**

Nucleic acid sequence derived from normal human gene sequence for AIPL1.

AIPL1 (aryl hydrocarbon receptor interacting protein like 1), is classed as a protein coding gene that is expressed in the rod and cone photoceptors. It is a photoreceptor/pineal-expressed gene that encodes aryl-hydrocarbon interacting protein-like 1 and is located within the LCA4 candidate region. The encoded protein contains three tetratricopeptide motifs, consistent with chaperone or nuclear transport activity. It has a critical role in cell viability and is required for the assembly of the phototransduction protein, phosophodiesterase in both rods and cones.

Mutations in the AILP1 gene cause approximately 20% of recessive Leber congenital amaurosis (LCA), a rare inherited retinal disease that causes nystagmus, severely impaired vision or blindness and an abnormal or flat electroretinogram in affected individuals. Individuals with LCA are usually diagnosed at birth or in the first few months of life, it for this reason that the use of this gene poses no threat to the operator.

RK-h is a promoter derived from the human rhodopsin kinase (RK) gene, which is active in both rods and cones. The RK-h promoter has been found to be highly efficient in driving reporter gene expression in both rods and cones and has been found to be highly specific for photoreceptor cells. The promoter is relatively small in size (under 300bp) and as such can be readily accommodated into AAV plasmid backbones that have limited packaging capacity.

Studies have found that the RK promoter is well suited for driving *AIPL1* transgene expression in photoreceptors for gene therapy purposes (Sun, *et al.* 2010, doi:10.1038/gt.2009.104)

Note: Species from which the nucleic acid sequences were obtained, whether a pest or pathogen, tissue (normal, tumour, healthy or diseased), health status of the donor, etc.

Name, description and function of the gene/nucleic acid sequences involved ("the insert")

Nucleic acid sequences within RK-hAILP1 are from Human, normal gene sequence for AILP1. AILP1 is located on chromosome 17p13.2 in humans and contains 6 exons

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Note: Biological function of the intact, natural gene; whether protein-coding sequence complete, partial, unknown, or known to be absent in construct; whether or not interrupted by introns etc; whether wild type or mutant; known, suspected or intended function of mutants; any other biological activities e.g. antisense, ribozyme, replication origin, mobilisation functions, etc. Genomic or cDNA library (consider the properties of the library as a whole; separate assessment is required for the specific clones you intend to isolate from the library).

Name and characteristics of the "vector"

The two plasmids used (RK-hAIPL1 in combination with pDG helper plasmid) are not being genetically modified themselves, they are simply a vehicle that allow the production and expansion of recombinant AAV in host HEK293 / HEK293T cells.

The RK-hAIPL1 are clinically viable plasmids, obtained from Professor Robin Ali at UCL.

The pDG helper and packaging plasmid plasmids were obtained from Plasmid factory (https://plasmidfactory.com/products/in-stock-service/aav-plasmids).

Adeno-assisted virus (AAV) / adenovirus hybrid plasmid, contains all of the packaging and helper functions required for production of recombinant AAV (rAAV). The pDG helper and packaging plasmid carries all genes essential for packaging of AAV-2 vectors into capsids of AAV-2 in HEK293 / HEK293T cells. This particular plasmid is the equivalent of pDP2 although it does not contain a heparin binding motif or the red fluorescent protein (RFP). The plasmid was derived from pTGMA after deleting 18323bp of Ad-5 sequences not required for rAAV production. See the attached paper by Grimm (1998) for more information on how the plasmid was derived.

The use of pDG as a helper plasmid means that the rAAV produced would no longer be dependent on over-infection of the cells with adenovirus and will also be helper-virus free; making it mobilisation defective and thereby reducing the potential risks associated with the use of adenoviral vectors (effects on the human respiratory and intestinal systems, eye infections and common colds).

Note: Name of parental plasmid, bacteriophage, etc; characteristics, i.e. mobilisable, mobilisation defective, non-mobilisable; host range; presence of drug resistance markers or other sequences of potential clinical or environmental significance. Whether constructs transferred into host cells e.g. as non-mobilisable DNA; presence of replication origins, conditional (e.g. SV40, EBV) or otherwise. Involvement of viral vectors (e.g. retrovirus, baculovirus); name, characteristics, whether replication defective and the basis of this (e.g. deletion); host range; pathogenicity; potential for complementation by products expressed in the host, or by superinfection, etc.

Name and characteristics of the "host"

See CBE/GMO/ 075 for all details regarding HEK293 / HEK293T cells.

Note: Species/strain etc, whether disabled/ highly disabled; presence of other agents which may e.g. assist transmission; or affect pathogenicity; any history of safe use; whether an intact multicellular organism is produced at any stage (e.g. transgenic animals, plants); if host is (a) cell line(s) derived from multicellular organisms, the species, any potential for harm to humans or the environment; presence of other agents which are themselves transmissible or may assist the mobilisation of the transferred sequences e.g. as a result of recombination.

Characteristics of the Genetically Modified (Micro)Organism

Will there be expression of the protein (or other functional product) encoded by the insert, in the genetically modified organism?

It is possible that AIPL1 will be expressed by the HEK293 / HEK293T cells. However, the process of AAV production and replication is destructive to the cells and only the AAV product will be harvested. As such, all of the remaining cells and debris will be treated as waste and will be disposed of in accordance with SOP003 "*Disposal of Biological Waste*".

Note: Provide details, e.g. of the promoter, level of expression, secretion, presence of introns within the coding region which might preclude expression of a functional product in E. coli, or other specific hosts, etc.

Specify any known or expected characteristics of the GMO which pose a risk to human health and safety and assess the severity and likelihood of such effects

Effects on human health (include colonisation, infection, allergy, toxin-mediated disease)
AVV is not associated with any human disease. However, there is suggestion of some effects of infection with AAV in the human embryo and male infertility. A significant correlation was found between the presence of AAV DNA in amnion fluids and premature amniorrhexis (rupture of the amnion) and premature labour [1], and an increased percentage of AAV DNA was found present in the testes of men with abnormal semen analysis – suggesting that it could possibly interfere with spermatozoa development. [1] Burguete, T., *et al.* (1999) Evidence for infection of the human embryo with adeno-associated virus in pregnancy, *Human Reproduction* 14(9) pp. 2396-2401 [2] Erles, K., *et. al.* (2001). DNA of adeno-associated virus (AAV) in testicular tissue and in abnormal semen samples. Human Reproduction. 16(11) pp. 2333-2337.
Humans at increased risk of the above effects (e.g. immunocompromised, pregnant or breastfeeding women)
Pregnant women, the immunocompromised

Note: Characteristics which might increase the pathogenicity of the GMO relative to the unmodified host, or decrease susceptibility to control measures, e.g. alteration in susceptibility to clinically relevant drugs or to immunological or other natural defences; any other potentially significant biological activities of encoded products, e.g. potential toxicity, allergenicity, growth promotion/inhibition, oncogenicity, other pharmacological activity, etc.

Does this project involve work with animals? Provide details

No.

Either use of transgenic animals or work with GMMs in animal models

Quantity of organisms to be used

Maximum level of cells produced across several T flasks is approximately 10^9 cells. This number of cells can produce an approximate10^12 vector.

Specify volumes and concentrations/culture density

Interim Assignment of Containment Conditions to Protect Human Health

Using the appropriate table(s) in Annex 1 of this form please select your control measures (you may place a **X** alongside each appropriate control measure to indicate that you have considered each one) and assign an interim level of containment for the work, i.e. ACGM containment level, (taking into account the hazard grouping of any biological agent). Please justify your decision to use this level of containment.
NB CLASSIFICATION OF THE PROJECT IS DEPENDENT ON ONLY THOSE CONTROL MEASURES THAT ARE SHOWN BY THE RISK ASSESSMENT TO BE NECESSARY TO PROTECT HUMAN HEALTH OR THE ENVIRONMENT. MEASURES THAT RESULT FROM CONVENTION, CONVENIENCE OR ARE REQUIRED FOR PRODUCT PROTECTION ARE NOT RELEVANT TO THE CLASSIFICATION See ACGM Newsletter 27/ACGM Compendium of guidance for further information

Interim containment level and corresponding Class (classes) of GMO(s) involved in the work (& explanation)

Work will be performed at CL2, the class of GMO is GMO1. Please see attached GMO classification of activity from gene therapy provider.

Note: You will need to consider the containment level necessary to control the risk of the host and then make a judgement as to whether the modification will result in a GMO more hazardous/less hazardous/about the same

Please provide the following information for the Committee:

Are any of the work procedures likely to generate aerosols? If so, is the work to be undertaken in a safety cabinet?

Some aerosols may be generated during culture, manipulation, transfection and pipetting of the cells.
A class II Biological Safety Cabinet will be used for all cell culture work to protect against aerosols or splashes.
All work will be carried out using aseptic techniques, maintaining a sterile environment for the cells and also protecting the operator and other users of the laboratory from biological agents using a class II biological safety cabinet.
Procedures to be carried according to the following SOPs:

1. SOP009, "*Use and Maintenance of HERASAFE KS Class II BSC*"
2. SOP104, "*Use and Maintenance of HERASAFE KS Class II re-circulating BSCs*"

Identify any use of sharps in the work; justify their use and specify control measures

None

Protective equipment and clothing to be used

1. Gloves:
    a. Disposable Nitrile powder free gloves for general use
    b. Autoclave gloves for use with the autoclave
    c. Cryogenic gloves to be used when handling Liquid Nitrogen
2. Side fastening white lab coats, with elasticated sleeves will be worn at all times during the lab
3. Shoe covers will be worn at all times during the lab
4. Face shields (primarily for handling Liquid Nitrogen)
5. Aprons or disposable lab coats for extra protection over Howie type lab coat when necessary
6. Laboratory safety glasses when necessary (including those for spectacle wearers)

Transport and storage arrangements

Cells will be stored in closed flasks within an incubator or in sealed vials in liquid nitrogen storage. If materials are to be transported between buildings, the biological agents will be transported in a sealed primary container and also in a secondary sealed container. For guidance on this, SOP005 "*Storage and Transport of Biological Agents*" will be followed. Refer also to Biological Risk Assessment.

Specify arrangements for safe storage; whether, and if so how, materials are likely to be transported between buildings, on public roads, or posted)

Disinfection

The disinfectants were carefully chosen for effectiveness in use. The number of disinfectants used is strictly limited to avoid errors and ambiguities in use and accidental mixing of compounds that may give rise to hazardous reactions or the formation of toxic products, namely avoid contact between Virkon and ChemGene. Unless there are compelling reasons to do otherwise, 1:50 Chemgene is the primary disinfectant used in laboratories alongside 70% IMS, which would be used for general disinfection (SOP004). For deep clean of BSCs, 1:20 ChemGene and 70% IMS are used and for disinfection of liquid waste 1% Virkon is used.

Both ChemGene and Virkon have a wide range of bactericidal, virucidal, mycobactericidal, fungicidal and sporicidal activities. Representative viruses from all the major virus families are inactivated by both ChemGene and Virkon. Working solutions of 1% w/v have low toxicity and no irritancy. Chemgene solutions are a potential skin and eye irritant and reacts with strong oxidizing agents (i.e. Virkon).
Selection and details in the following SOPs:

1. SOP004 – "*General Laboratory Housekeeping*"
2. SOP006 – "*Selection and Use of Virkon Disinfectant*"
3. SOP039 – "*Storage, Handling and Disposal of Chemicals*"
4. SOP160 – "*Preparation and use of ChemGene disinfectant for use in the CBE labs*"

CBE/COSHH/242 Risk Assessment for the preparation and use of ChemGene HLD4
CBE/COSHH/039 Risk Assessment reference for Virkon

For hazard group 1 and 2 biological agents it is normally sufficient to rely on the manufacturer's data providing the recommended concentrations and contact times are used. Hence 1:20 and 1:50 Chemgene and 1% Virkon is used per manufacturer's instructions and according to the local code of practice and SOP006- "*Selection and Use of Virkon Disinfectant*", SOP160 - "*Preparation and use of ChemGene disinfectant for use in the CBE labs*".

Independent studies have reported that 1% Virkon completely destroys a wide spectrum of organisms within a contact time of 10 mins.

Specify disinfectant(s) to be used, and their dilution. Have these been validated for use with the relevant organism?

Inactivation of GMMs in waste, and subsequent disposal

Cell culture liquid waste will be disinfected for 24hrs with 1% Virkon then waste is poured down the sink with copious amounts of water. These disinfectants are well known the be effective against a wide range of viruses, fungi and bacteria. For Hazard Group 1 and 2, it is sufficient to rely on data from the manufacturer, providing the recommended concentrations and contact times are used.

For solid waste, such as tissue culture plastic and other consumables, decontamination by autoclaving will be carried out following the appropriate SOPs. The autoclave is a validated method of decontamination of biological waste, using cycle 4 for solid waste, minimum 121°C for 15 minutes. Treatment cycle (4) is validated according to SOP024 "*Maintenance of Systec VX-95 Autoclave CBE044*". Annual validation is conducted by an external contractor, validation of individual cycles is performed using autoclave tape monitors.

Decontamination will be performed with procedures outlined in SOP003 "*Disposal of Biological Waste*". The procedures outlined are expected to generate 100% degree of kill.

The Contained Use Regulations 2000 require that GMMs in contaminated material and waste are inactivated by validated means. You must specify the METHOD of inactivation of the GMMs, the expected DEGREE OF KILL of the GMM achieved by that method, and the VALIDATION of that method.

Monitoring of Containment and Control Methods

Monitoring of containment at point of use

Not required as HEK293 / HEK293T cells will not survive outside a highly specialised environment.

Monitoring of waste inactivation methods

According to procedures detailed above and in attached biological risk assessment.

Emergency procedures - Is an emergency plan required? Provide details (or attach)

No

Note: In the event of a reasonably foreseeable accident where the health and safety of people outside the premises is liable to be seriously affected or where there is a serious risk of damage to the environment then an emergency plan is required. This plan may need to be communicated to the emergency services and other relevant bodies. In most cases this will only be required for Class 3 and 4 projects (See ACGM Newsletter 27/Compendium of Guidance for further information). However, details of accident/spillage procedures should be provided for all projects.

Occupational Health issues

See CBE/GMO/075 for details relating the HEK293 / HEK293T cell line.

AVV is not associated with any human disease.

However, there is evidence of AAV infection in the human embryo and an association of AAV with male infertility. Recombinant AAV vectors lose site specific integration into chromosome 19, thereby raising the theoretical concern of insertional mutagenesis.
There is a theoretical risk present of infection from exposure to laboratory cultures of wild-type adeno-associated virus or recombinant viruses, although in this project, only recombinant AAV will be produced; thereby reducing the risk considerably. Transmission of AAV can occur through ingestion, inhalation of aerosolized droplets, mucous membrane contact and accidental injection.

No specific requirements for immunisation or health monitoring is required. The transfected cells will be handled in CL2 laboratories at all times and will be used within a class II biological safety cabinet. In addition, all personnel involved on the project will wear the correct personal protective equipment and follow local COP and SOPs to mitigate risks.

Specify any requirements for immunisation, chemoprophylaxis or health monitoring, and any special requirements for record keeping

Environmental Considerations

ANSWERS MUST BE JUSTIFIED IN SOME DETAIL, i.e.- IT IS NOT ACCEPTABLE TO SIMPLY STATE THAT THERE IS NO RISK TO THE ENVIRONMENT.

Risk to animals, fish, plants etc

If the recipient microorganism is controlled by DEFRA, do you have a DEFRA licence? (delete as appropriate)	**N/A**

Approval will not be granted until a copy of the DEFRA licence (if applicable) has been submitted to both the local GMSC and the Advisory Group for the Control of Biological Hazards

Identify any identifiable potential hazards to the environment, which might occur if the genetically modified organism were to be accidentally released. Classify the potential hazard as Severe, Medium, Low or Negligible.

HEK293 / HEK293T cells – Low hazard, viral replication does not occur in immortalised cells because they do not contain the origin of replication.

Recombinant AAV – Medium / Low hazard, recombinant AAV vectors can infect a wide range of cell types from a variety of mammalian cells but is known to not cause disease in humans.

The transfected cells will be maintained within the CL2 laboratories at Loughborough University and will be used within a Class II biological safety cabinet.

Note Potential hazards might be identified, and their severity assessed, dependent upon: the host species, the vector or the insert; or phenotypic changes caused by the genetic modification; the presence of host or susceptible species in the environment; the potential for survival, multiplication and dissemination in the environment; the stability of the GMO in the environment; the possibility of gene transfer to other species, etc. Refer to ACGM Compendium of guidance for further information

In view of the characteristics of the GMO, specify the likelihood of accidental release and occurrence of the above mentioned potential harmful effects, if the work were to be performed at the interim containment level specified above. Classify this as High, Medium, Low or Negligible.

Low

Note: This includes the wider as well as the local environment in which the activity is to be carried out. Consideration should be given to any potential exposure of the environment to the GMMs and the magnitude and duration of such exposure. Refer to ACGM guidance for further information

Grade the overall Risk to the environment (= Potential harm x Likelihood) as High, Medium, Low or Effectively Zero.

Low

Additional Containment

If, in considering the potential for harm to the environment, you have concluded that the Risk to the environment is high or medium, then the containment conditions previously specified may need to be modified to reduce the risk to an acceptably low level. Use these considerations to revise your provisional containment level so that all risks are controlled to low or effectively zero.

Additional containment provisions for environmental protection

N/R

Assign your final containment level.

Work will be performed at CL2, the class of GMO is GMO1. Please see attached GMO classification of activity from gene therapy provider.

Are all hazards now controlled by this proposed level of containment?	**Yes**

Final classification of the activity, i.e. Class 1/2/3/4. Is the activity notifiable to HSE?

Class 1 activity, not notifiable.

Where the containment and control measures fall between two levels, e.g. where level 1 is appropriate with some control measures from level 2, the classification for the activity is equivalent to the HIGHER containment level. All Class 2,3 and 4 projects are notifiable to the Health and Safety Executive through the Health and Safety Unit

Do you intend to apply <u>all</u> control measures from your highest selected level of containment (See Annex 1)**? If not, please justify the exclusion of any control measures not used.**

Yes

Formal application to the Health and Safety Executive is required for derogation from the full containment level for all Class 2, 3 and 4 projects.

EC Regulation requires notification of transboundary movements of Class 3 GMMs to the Biological Clearing House and European Commission** ***(transboundary movements are those entering or leaving the EC)**. **If your work involves Class 3 GMMs please indicate below whether they will be subject to transboundary movements.

N/R

Workers Involved in the Project and Facilities Used for the Work

Please indicate the areas where work will be carried out (including Room No. and Designation):	
Room No. and designation	**ACGM Categorisation**
Centre for Biological Engineering, Holywell Park, Loughborough University	CL2 Facilities

Workers initially involved in work:	Post/experience/training:
A. E. Evans	Documented in personal training file. Manual cell culture experience.
Training and assessment of competence for existing and future personnel *Specify arrangements for provision for existing and future personnel*	

Authorisation and Notification

The work proposed should be discussed with the Departmental Biological Safety Officer.

Signature of proposer ..... **Date** 21/11/201

Please print name A. E. Evans

E. Ratcliffe 20/11/2017

Other Signature (s) (if required – please state position) ..... **Date** .....

Please print name E. RATCLIFFE

Signature of Biological Safety Officer or authorised Deputy ..... **Date** 3/3/18

Please print name .....

NB The Approval of the University's relevant Safety Committee is required before work starts.

APPROVAL of the RELEVANT SAFETY COMMITTEE

On behalf of SC ..... **Approval Date** 3/3/18