Retrospective Review of Project Licences

Project Licence Retrospective Review

"The overall purpose of retrospective review in the general sense of '*following the development and outcome of projects'* is, wherever possible, to reduce the harms and increase the benefits of every project at an establishment. The aim is to improve both animal welfare and the quality of science and to help inform future debate on these issues." [RSPCA and LASA, 2015, Guiding Principles on Good Practice for Animal Welfare and Ethical Review Bodies. A report by the RSPCA Research Animals Department and LASA Education, Training and Ethics Section. (M. Jennings ed.)]

At the University of Cambridge one (or possibly more) of the following will determine when your licence will be requested for review:

a. 12 to 6 months before your existing licence is due to expire if you have no plans to write a new licence;
b. 15 to 12 months before your existing licence is due to expire if you plan to write a new project licence;
c. 3 months before you terminate your licence if you intend to revoke your licence before its due expiry date;
d. When there is a change of project licence holder (in this case the person currently holding the licence should complete the retrospective review before the amendment is made to change the project licence holder);
e. As determined by the AWERB Standing Committee. The AWERB Standing Committee may decide a licence should be reviewed at a specified time or times based for example on the severity of the work, novelty of the models etc..

The information you provide in or attached to this document must reflect data generated only from work carried out under the licence under review. Please do NOT copy and paste text that appears in your current licence unless requested to do so.

You are not restricted by the size of the text boxes on this form; they are designed to expand to accommodate your text. However please remember that AWERB Standing Committee members, which will include your colleagues, have to review the information you provide so please be informative and concise and do not include information that is not requested. Please remember to use Plain English, where possible.

Please be aware that Retrospective Reviews, as with your current and previous project licences, can be requested under the Freedom of Information Act 2000. It is therefore wise to take care when completing this document and ensure that it does not contain typographical errors, personal details or any sensitive information pertaining to Intellectual Property.

A copy of the final agreed version of this document and any advice provided by the University AWERB in relation to this document will be forwarded to your local Home Office Inspector.

If you use abbreviations could you please ensure the first time the abbreviation is used that it is spelt out fully with the abbreviation in brackets.

Finally, if Home Office has identified your licence as one that required a Retrospective Assessment please still complete this template. The information gathered will be used by AWERB to undertake their required task to review your work and can be used to complete the Home Office Retrospective Assessment template. The latter can be achieved by copy and paste will a further update just before submission to include work you have complete between when you fill in this template and the expiry of your licence, which is when your Retrospective Assessment will need to be sent to the Home Office.

Thank you.

1. General Information:

Project licence holder to complete if information provided is incorrect

Name:	Professor John Doorbar	Nagayasu Egawa
Contact details: Address & tel.	Department of Pathology, University of Cambridge Tennis Court Road, Cambridge, CB2 1QP +44-12233333335	Department of Pathology, University of Cambridge Tennis Court Road, Cambridge, CB2 1QP +44-12233333335
Project No.	PP6137009	
Project title	Papillomavirus Transmission, Infection and Lesion Formation	
Project purpose	To establish how papillomaviruses are transmitted, how lesions form and are maintained, and to find new ways to prevent transmission and treat and treat clinical disease.	

Date licence was granted	18th November 2020
Date of retrospective review is sent to the PPLh	05th September 2024

The following are the triggers for licence Retrospective Review:
If you are completing this form because you have been asked to complete a Retrospective Review and our UBS staff have completed this box for you. Please check that you agree with the selection made and correct if you believe the information is incorrect.

A	X	My licence is due to expire in 6 to 12 months time and I have no plans to write a new licence
B		My licence is due to expire in 12 to 15 months time and I plan to write a new project licence to continue my research
C		I plan to request the revocation of my licence before its natural expiry date
D		I will no longer be the project licence holder but another person will continue to hold the licence. **The name of the new licence holder will be**:
E		I took over this licence from (insert name) in (insert date)
F		The AWERB Standing Committee has asked for this Retrospective Review.

Note to licensees:
In the case of **option D** if the new project licence holder's name has not been filled in please add this information to this box.
In the case of **option E** please insert the name of the person from whom you took over this licence and the date when you became licence holder.

2. Animal Welfare/Recorded Harms:

2.1 Using the table below please provide the information requested.
How to complete this table: Return of procedures count animal numbers from 1st January to 31st December. In the table below if your licence was granted part way through the year count year one as the time from when the licence was granted to the 31st December of that year. Year two will be from January to December etc. until the final year for which the report is requested and count from 1st January to the requested report date. You can insert rows as necessary. For any animals that experienced a higher level of severity than that of the protocol please highlight these figures in **bold.** The figures provided can be obtained from your Home Office returns.

Protocol No.	Species	Protocol severity category	Total est. number	Actual number used	Actual severity recorded					
					Non-recovery	Sub Threshold	Mild	Moderate	Severe	Totals
1	Mouse	Mild	2000	1st year						0
				2nd year						0
				3rd year						0
				4th year						0
				5th year						0
				6th Year						0
				Total						0
2	Mouse	Mild	250	1st year						0
				2nd year						0
				3rd year						0
				4th year						0
				5th year						0
				6th Year						0
				Total						
3	Mouse	Mild	100	1st year						0
				2nd year						0
				3rd year						0
				4th year						0
				5th year						0
				6th Year						0
				Total						0
4	Mouse	Moderate	40	1st year						0
				2nd year						0
				3rd year						0
				4th year						0
				5th year						0
				6th Year						0
5				Total						0
	Mouse	Moderate	20	1st year						0
				2nd year						0
				3rd year						0
				4th year						0
				5th year						0
				6th Year						0
				Total						0
6	Mouse	Mild	1200	1st year						0

				2nd year						0
				3rd year						0
				4th year						0
				5th year						0
				6th Year						0
				Total						0
7	Rabbit	Mild	100	1st year						0
				2nd year			2			2
				3rd year			12			12
				4th year						0
				5th year						0
				6th Year						0
				Total						14
				1st year						
				2nd year						
				3rd year						
				4th year						
				Total						
									Whole Total	

*If actual severity data has not been formally assigned at the point the Retrospective Review is undertaken, the columns can be used to indicate the estimated severity for each of the categories.

2.2 Does the information provided in the table reflect the projected incidence of harm provided in the adverse effects for each protocol? If not please indicate where this was not the case and whether the projected level of suffering was more or less than you anticipated when you first wrote the licence. If the severity category for a protocol was amended during the tenure of the licence please include this information in the reasons box.

Protocol number	Severity higher/ same/ lower than anticipated	Reason
N/A		

2.3 Describe any unexpected adverse effects and include the percentage and the number of animals affected. How were these episodes managed and recorded? If any of these resulted in a Project Licence Standard Condition 18 report please indicate which were reported under Condition 18 and the date (also see Section 5.2).

N/A

2.4 What percentage and number of animals had to be killed or died unexpectedly before the end of the experiment? Please provide a brief summary of each incident by protocol(s) where this occurred.

Protocol No.	% and number of animals killed or unexpectedly found dead
7	2 rabbits in Year 2. During the procedure conducted at the Bancroft facility, one of the rabbits developed diarrhoea and began to lose weight shortly after the experiment started.

	As recovery was considered unlikely, the procedure was terminated before the animal reached the predefined weight-loss endpoint. Because the procedure was performed as a pair, both animals were culled. It was concluded that there was no causal relationship between the procedure and the diarrhoea or weight loss.

2.5 Were your estimated animal numbers accurately reflected in your actual animal usage as provided in Table 2.1 above? ~~**YES**~~ **NO**

If no, please explain the why there was a difference. Please do this on a protocol by protocol basis.

Protocol No.	If your numbers were less that estimated please explain why.
1-6	The mouse components of the Project Licence were not carried out. The reasons are as follows: For the lesion-formation studies: (A) The project did not reach the stage within the licence period where the planned mouse experiments were to be conducted, as the overall research programme progressed more slowly than anticipated. (B) Attempts to secure the necessary funding were unsuccessful. (C) In addition, a different funder (other than those in points A and B) did not agree to proceed with the mouse-based phase of the study. For the transmission studies: (A) Although funding was available, the work could not be conducted as planned because of the impact of the COVID-19 pandemic, which led to changes and delays to the planned schedule.
7	For the rabbit components of the project: (A) A pilot study was conducted; however, based on its outcome, further rabbit work was not required or justified within the duration of this licence. (B) We have been analysing archived rabbit lesions, and the project has not yet reached the stage where new in vivo experiments would be necessary.

2.6 Have you re-used animals? ~~**YES**~~ **NO**

If so, why have you re-used animals and what has been the impact of re-use on the welfare of your animals? Please also provide the species and number of animals re-used by protocol where re-use occurred.

Species	Protocol No. on which animals where/will be returned as re-used, why and what impact, if any, this re-use had on the welfare of your animals
N/A	

2.7 Has there been any animal wastage? ~~**YES**~~ **NO**

For example, this may occur when breeding and maintaining genetically altered animals or when animals have been ordered and cannot be used for some technical reason.

Where wastage has occurred, please explain the circumstances and nature of the wastage plus an indication of the numbers of animals. Please also provide either the number or percentage of animals that were wasted.

Circumstances and nature:

Estimated number or percentage of animals wasted and if appropriate provide this information by protocol:

2.8 For licences that authorise the breeding and maintenance of genetically altered animals:

a) explain how you optimise breeding efficiency, and
b) explain what use is made of any excess stock animals, and
c) explain if, and how, you have used any transgene repository – national, international, or internal.

N/A

2.9 If you breed genetically altered animals are your strains recorded on a database (e.g., MCMS) that can be

a) accessed by other researchers at the University? **YES NO**
b) accessed by researchers outside the University? **YES NO**
c) would you allow other researchers at the University to use your strains? **YES NO**
d) would you allow external researchers to use your strains with an MTA applied? **YES NO**

If you have answered YES to any of these questions please elaborate below:

N/A

If you have answered NO to any of these questions please explain why.

N/A

2.10 Have you been able to refine and/or reduce the impact of contingent harms arising from your use of animals (contingent harms are harms for example that arise from the transportation of animals, single housing animals or housing animals in non-Code of Practice accommodation, etc.). ~~**YES**~~ **NO**

Please explain/provide examples.

2.11 By species and percentage please indicate the source of your animals.

Species	Source	Approx. percentage
Rabbit	Charles River	100%

2.12 During the tenure of the licence have you requested an amendment to increase/decrease animal numbers? ~~**YES**~~ **NO**

If so which protocols were amended and were numbers increased or decreased, and by how much?

Protocol No.	Original estimated Number	Amended estimated number

If you have increased or decreased animal numbers please explain why this was necessary?

N/A

2.13 During the tenure of this licence have you requested an amendment to increase/decrease the severity of any protocols? ~~**YES**~~ **NO**

If so which protocols were amended and were the severity categories increased or decreased?

Protocol No.	Original severity category	Amended severity category

If you have increased or decreased the severity category of any of your protocols why was this necessary?

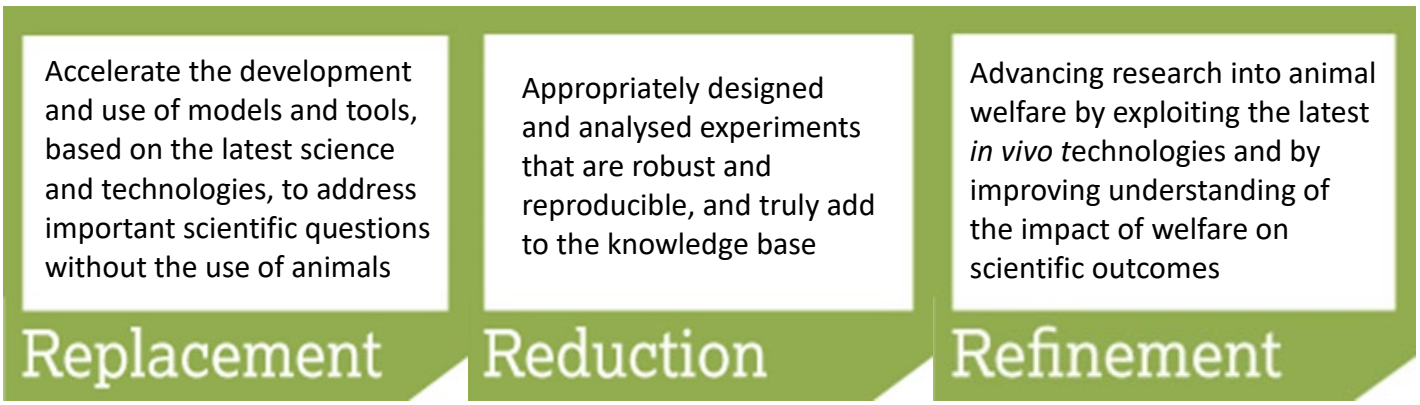
N/A

3. **3Rs:**

In this section, please explain what steps you have taken during the tenure of your licence that resulted in 3Rs gains. This might include working with collaborators to refine your model, changing the anaesthetic regime or equipment, etc. Consider every change you have made and its impact on the 3Rs – even small changes and initiatives can result in 3Rs gains.

The following definitions come from the NC3Rs website and are included to help you provide information under the most appropriate R below:

Definitions



3.1 Have you attempted or been able to replace any of your techniques or models with non-animal alternatives? ~~**YES**~~ **NO**

Please explain.

At this stage, replacement was not applicable.
The mouse work did not proceed because the project never reached the point at which in vivo studies were required.
For the rabbit work, only the minimum necessary pilot study was conducted, and the project did not advance to stages where alternative (non-animal) models could be meaningfully considered or evaluated.

3.2 Have you been able to reduce your animal usage? ~~**YES**~~ **NO**

If so, how have you achieved this (e.g., through experimental design, changes to the regulated procedures used)? Please give an indication of the actual numbers reduced.

N/A

3.3 Are you involved with any tissue sharing either within the University or more widely?

Please explain:

N/A

3.4 Please **LIST** the techniques and/or animal models you have used on your licence (include GA models). Later on you will be asked about the 3Rs achievements – please **do not** detail your 3Rs achievements in this box.

N/A

3.5 How successful have these techniques and/or models been?

The papillomavirus infection and observation studies in rabbits were carried out exactly as anticipated, and the results were fully consistent with expectations.

3.6 What limitations, if any, have you encountered? Were you able to overcome these limitations and, if so, how?

N/A

3.7 Have you attempted or been able to refine any of your techniques or models?

~~**YES**~~ **NO**

Please provide a list of techniques or models you have been able to refine and the refinements you have made. Please indicate if you have published or disseminated this information during the tenure of this licence and attach a copy of the publication.

N/A

3.8 Do you use systems to monitor the welfare of your experimental animals (e.g., scoring sheet)?

YES ~~**NO**~~

If not, why?

If you do use a welfare monitoring system, what do you use? Did you refine or modify your system during the tenure of your licence and what impact did this have?

During the experimental period, we used the monitoring system provided by the facility for welfare assessment of the rabbits.
No refinements or modifications were made to this system during the tenure of the licence, and therefore no impact on the monitoring process is reported.

3.9 Were the end points detailed in your project licence appropriate? **YES** ~~**NO**~~

Have you needed to modify them during the tenure of your licence? ~~**YES**~~ **NO**

Please explain.

N/A

3.10 Please review the non-schedule 1 methods of killing authorised on the protocols on your licence. In the box below, list each method and beside each clearly indicate which you have used? Examples of non-schedule 1 methods include: exsanguination, decapitation and perfusion fixation.

• Overdose of anaesthetic followed by confirmation of death – used during the rabbit pilot study. No other non-schedule 1 methods authorised on the licence were used.

Were these killing methods the most refined? **YES** ~~**NO**~~
Were they the most appropriate for your experimental data? **YES** ~~**NO**~~

If you have answered NO to either of the above questions please explain. If you were able to refine the way your animals were killed please explain how this was achieved.

N/A

3.11 Have you received awards or funding specifically targeted at the 3Rs? ~~**YES**~~ **NO**

If so what was the source of your funding, when did you receive it and what did the funding allow you to achieve?

N/A

The AWERB 3Rs committee is particularly interested in this section of your review because information you provided here could be of interest and use to other researchers at the University.

Information that you have included in this section will be included in the UBS 3Rs Search Tool unless you complete the box below. UBS will only add information to the UBS 3Rs Search Tool section on the UBS website that University staff can log into using their Raven Access. You should however disseminate all 3Rs finding more widely.

I do not agree to information provided in this section to be added to the UBS 3Rs Search Tool for the following reason(s).

4. Scientific Progress and Benefit Achievements:

4.1 Taking into consideration that your licence may not be due to expire, has your research progressed as you expected? **YES NO**

4.2 When your licence is due to expire will you have completed the programme of work described in this licence? ~~**YES**~~ **NO**

4.3 Regardless of whether you managed to complete your programme of work, what have you achieved/discovered during the time since this licence was granted? (Please copy your key scientific questions/objectives which appear at the beginning of Part D, or in the Action Plan, of your project licence into the box below and against each explain what you have achieved/discovered).

Objective 1
Do variations in virus preparation (purified, cell-free or virus in squames) behave differently during transmission?
Achievement:
Progress on this objective was significantly affected by the COVID-19 pandemic and changes to the wider research plan.
As a result, the project did not reach the stage at which comparative transmission experiments using different virus preparations could be carried out.
Only preliminary validation of the rabbit infection model was possible under this licence.

Objective 2
What molecular processes are required to form/maintain the papillomavirus lesion?
Achievement:
A pilot study using the rabbit model was successfully conducted and behaved as expected, providing preliminary confirmation of lesion development dynamics.
However, further in vivo studies—intended to progress to molecular analyses and lesion maintenance studies—were not reached.
The project could not advance to these stages due to lack of available funding for the subsequent planned work.

Objective 3
How do papillomaviruses behave at different sites of infection?
Achievement:
As with Objective 2, only the initial pilot rabbit work was completed.
The project did not progress to the point where comparative site-of-infection studies could be initiated.
This was due both to the programme not reaching the required stage and to the absence of funding to support the next phase of work.

Summary
Across the objectives, a rabbit pilot study was completed and performed exactly as predicted, confirming the expected behaviour of papillomavirus infection in vivo.
However, the wider programme did not reach the stages where the planned transmission, molecular, or site-specific studies could be undertaken.
Pandemic-related disruption, changes to research priorities, and limited funding prevented further progression during this licence period.

4.4 For key scientific questions/objectives you could not complete either fully or partly, please include an explanation as to why you were not able to achieve what you set out to achieve when the licence was granted (reasons could for example include lack of funding, the model took longer than expected to develop, another group published data which meant continuing the work would equate to repeating the work, etc.).

The programme did not advance to the stages required to complete Objectives 1–3.

The reasons are summarised as follows:

- COVID-19–related disruption and changes to the overall research plan prevented progression into the planned transmission studies (Objective 1).
- Lack of available funding meant that the project could not move beyond the initial pilot work in rabbits (Objectives 2 and 3).
- The project as a whole did not reach the stage at which further in vivo studies (mouse or rabbit) were required, due to delays in upstream research activities.

As a result, only preliminary rabbit pilot studies were completed, and the planned downstream stages could not be initiated within the period of this licence.

4.5 In the expected benefits section of your licence you described the benefits you believed would be likely to arise from your programme of work. Please explain what benefits have actually been achieved and, if appropriate, explain how these differ from what you anticipated you could achieve when you wrote the licence.

No direct scientific or translational benefits described in the expected benefits section of the licence have been achieved during the period of this licence.

Although a rabbit pilot study was successfully completed and confirmed expected behaviour of papillomavirus infection in vivo, the project did not progress to the stages at which the anticipated benefits—such as insights into transmission, lesion biology, or site-specific infection processes—could be realised.

This differs from the original expectations because the programme did not advance as planned due to funding limitations, delays in upstream research, and pandemic-related disruption.

4.6 Specifically, if you were unable to address any or even all your key scientific questions/objectives what impact did this have on the benefits arising from your work?

Because the key scientific objectives could not be addressed beyond the initial rabbit pilot study, the anticipated benefits described in the licence were not realised.
The inability to progress to the planned stages—such as comparative transmission studies, molecular analyses of lesion formation, and site-specific infection studies—meant that no substantive scientific or translational outcomes were generated during this licence period.

As a result, the potential benefits originally expected from the programme were not achieved.

4.7 Were you able to identify/develop/implement any new scientific or technical developments during the tenure of this licence? ~~**YES**~~ **NO**

If so, what were these and what were/was the benefit(s)?

N/A

4.8 Using the headings below please provide a list of publications and meetings attended where **research arising from work undertaken under this licence** has been disseminated.
Please highlight in bold the publications which contain and meetings at which 3Rs achievements were disseminated.

Please only include publications arising from research undertaken under the authority of this licence. If you have papers in press please include these.

Publications in scientific journals: N/A
Publications pending, or under review: N/A
Presentations at scientific meetings: Work related to the rabbit pilot study was presented at the International Papillomavirus Conference (IPVC) 2024 in Edinburgh.

Have you remembered to highlight in bold the publications which contain and meetings at which 3Rs achievements were disseminated?

4.9 Have you engaged with the general public by giving interviews about your work on radio, television, at a public meeting or debate or in a newspaper article? ~~**YES**~~ **NO**

If you answered NO: why?

NO — Public engagement activities were not undertaken because the project did not progress beyond the initial pilot stage, and no substantive scientific findings were generated that would be appropriate for public dissemination.

If you answered YES: how, where (i.e., what medium did you use) and when did you engage with the public, what sort of information did you disseminate and what was the outcome?

5. Project Licence management information.

5.1 Amendments (if applicable):
Provide dates and a summary of all amendments made to this licence (i.e., what each amendment requested and why it was required) since the licence was granted (or if appropriate since the licence was last reviewed).
Please read questions 2.11 and 2.12 – for amendments that apply to this question including those that apply to either 2.11 or 2.12, please provide the date of the amendment here and, if relevant, a note that further information can be found in Section 2.11 or 2.12.

N/A

5.2 Project licence Standard Condition 18 Reports (if applicable):
Provide dates and copies of all Condition 18 reports sent to the Home Office since the licence was granted (or if appropriate since the licence was last reviewed). Copies of any reports should be attached/supplied as separate documents please.

N/A

5.3 Non-Compliance (if applicable):
Provide the date, a summary of the nature of any non-compliance and the outcome (or if appropriate since the licence was last reviewed).

N/A

5.4 Compliance Assurance Meetings [CAMs] or Root Cause Analysis (RCA) meetings (if applicable):
Provide the date, a summary of the nature of any incident and the outcome, if known (or if appropriate since the licence was last reviewed).

N/A

5.5 Have there been any other issues that have affected the management of this licence that you feel should be taken into consideration, (e.g., equipment failure, absence of key staff, change in the health status of the animal unit etc.)?

N/A

6 Retrospective Review:

Project Licence Holder check list:

AWERB requires the following documents	Documents sent to AWERB
Completed copy of this form	
Copies of Condition 18 reports (if applicable)	
Copies of 3Rs publications (if applicable)	

For UBS office use only:

	Date
1. Retrospective review form sent to project licence holder	05/09/24
2. Retrospective review form received by the Project Support Team	
3a. Project Support Team meeting	
3b. 3Rs committee	
3c. AWERB Standing Committee	
4. Process completed	