UNIVERSITY OF CAMBRIDGE
University Biomedical Services

For Office use only, enter Number:
T

UNIVERSITY OF CAMBRIDGE AWERB REQUEST

Application for non-regulated use of animals in teaching

(To be completed electronically)

Name of applicant: Sergio Tomey / Ewan Smith
Applicant's e-mail: st474@cam.ac.uk / es336@cam.ac.uk
Applicant's mobile number: 01223334046
Applicant's qualifications and experience: Tomey: Zoology BSc (Hons). Senior Chief Teaching Technician – 4 year and 6 months (from Jan 2019). Senior Teaching Technician - 4 years and 1 month (from Dec 2014 to Jan 2019). Competency for Schedule 1 Euthanasia. Home Office License Course Modules 1 (2019). Smith: Worked with animals in research since obtaining Home Office Personal License in 2001. Has held 3 project licenses (70/7705, P7EBFC1B1 and current PP5814995). Core Scientist on University of Cambridge AWERB since 2018.
Applicant's professional address (University of Cambridge Department): Department of Pharmacology.
Name of applicant's supervisor (if applicable): Nadine Law for Sergio Tomey
Department in which the animal(s) are to be kept (if applicable): Guinea-Pigs: CAF
Place/Department where the teaching will take place (include Department, Designated room number): Teaching laboratory. Ground floor. Department of Pharmacology.
Species, number, life stage, sex and strain of animal(s): Michaelmas term: 30 Guinea-pigs (female Dunkin Hartley). 300-350 grams. Lent term: 10 Guinea-pigs (female Dunkin Hartley). 300-350 grams. **Totals for the whole academic year 2023/24:** 40 Guinea-Pigs (female Dunkin Hartley).
Source, amount and duration of funding for this teaching programme. Has your funding been peer reviewed and if so, by whom and when? Departmental Teaching Budget
A "regulated procedure" is defined as any experimental or other scientific procedure applied to a protected animal that may have the effect of causing that animal pain, suffering, distress or lasting harm.

"Pain, suffering, distress and lasting harm" encompass any material disturbance to normal health (defined as the physical, mental and social well-being of the Animal). They include disease, injury and physiological or psychological discomfort, whether immediately (such as at the time of an injection) or in the longer term.

Regulated procedures may be acts of commission (such as dosing or sampling) or of deliberate omission (such as withholding food or water).

Why do you believe this teaching programme proposal does not require Project Licence authority under the Animals (Scientific Procedures) Act 1986.

This work does not require Project Licence authority because animals will only be used for collection of tissues to support teaching (and research) following a Schedule 1 procedure.

Have discussions with the Home Office inspector taken place (if so, please give details of with whom and when):

What are the learning objectives of this teaching programme?
For students to:

Attain a core knowledge in basic pharmacology, and so lay a secure foundation in the principles of drug action to support future courses in medicine and veterinary medicine, which students will carry with them into their professional careers.

Develop their experimental and data analysis skills through a range of experiments carried out in the practical laboratories and attendance at demonstrations and supervisions.

Gather knowledge enabling them to explain the principles of ligand-receptor interaction, local and intracellular messengers and integration of signalling pathways.

Learn to identify the major classes of drug receptors and sites of drug action within the body, as well as the biological variation that arises between individuals.

Identify typical examples of drugs that can be used to restore physiological functions in the cardiovascular, renal, respiratory, digestive, reproductive, peripheral nervous and central nervous systems.

Demonstrate an understanding of the use of drugs to control inflammation and immune responses, or to kill bacteria, viruses, parasites or malignant cells.

Apply the basic principles that govern the absorption, distribution and elimination of drugs to predict the time course of drug concentrations in the body and consider the implications of these principles for the therapeutic use of drugs.

Recognise the fundamental methods used in pharmacological research and be able to use basic pieces of research equipment.

Who is this teaching programme aimed at (e.g. Part II Pharmacology students)?

MedST/VetST 1B Mechanisms of Drug Action (MoDA).
NST 1B Pharmacology.

Does the use of animals or animal tissues form an integral part of a University course? Yes

What are the anticipated benefits arising from this teaching programme?

Pharmacology deals with the effects of chemical substances on biological material and thus has roots in both the physical and biological sciences. The NST1B Pharmacology Course is intended to emphasise the basic mechanisms of drug action in relation both to drug-receptor interactions and to the operation of physiological and biochemical systems. It provides the foundation needed for the harnessing of our understanding of how drugs work for the successful development of drugs in the future.

The MedST/VetST 1B Mechanisms of Drug Action course aims to provide an understanding of the basic mechanisms of drug action at the levels of both drug-receptor interactions and the effects on body systems. Attention is focused not only on the current use of drugs, but also on a framework for evaluating future therapies and to become familiar with the hands on, practical aspects of biological variation between individuals.

How will the use of live animals or animal tissue support the teaching objectives and outcomes?

It is difficult to teach students about how biological tissues behave without hands on experience with live tissue. Live tissue responds to handling in a way in which no other substitute does and displays the biological variation that simulations are unable to do.

Students see the phenomena described within the lecture series as part of the practicals, but also - more importantly - they see how their particular preparation differs from the ideal 'textbook' response'. They also see how neighbouring preparations also differ. This variability is not described well in any of the standard textbooks or in simulations that have been developed where every tissue is "perfect".

They also experience how live tissue behaves - the different forces that can be applied without functionally damaging the tissue. It also introduces the students to difficulties in making certain measurements - again something which needs to be experienced at first hand and is better conducted with live tissue than with simulations where one can simply "re-set and repeat", i.e. factors such as receptor desensitization and irreversible tetanus are important factors to consider when planning how to conduct experiments with live tissue.

The coupling of the live preparation with live demonstrator help provide a learning experience beyond that which can be delivered by the most sophisticated simulation or video.

During 2020/21 a survey of all current 2nd and 3rd year NST and MedST/VetST students was conducted and the report submitted to AWERB – to quote from the summary of that report:

"*In summary, although online practical classes have run smoothly and in general been a success in the academic year 2020/21, they are a poor replacement for the breadth of the learning experiences that arise from conducting practical classes with animal tissue, in particular because the procedural learning element of interacting with physical apparatus, generating one's own data and witnessing the diversity of responses in animal tissue (as happens in research and clinical practice).*"

At the advice of AWERB, a second survey conducted in 2021/22 concluded:
• "2nd year students feel that practical classes using animal tissue led to better development of experimental, data generation and data analysis skills than online practical classes"
• "2nd year students feel that practical classes using animal tissue were more engaging than online practical classes"
• "2nd year students feel that practical classes using animal tissue have better prepared them for conducting a research project in year 3"
• Of those third year students conducting research projects, "students feeling that such in person practical classes with animal tissue would have better prepared them for conducting a research project in year 3"

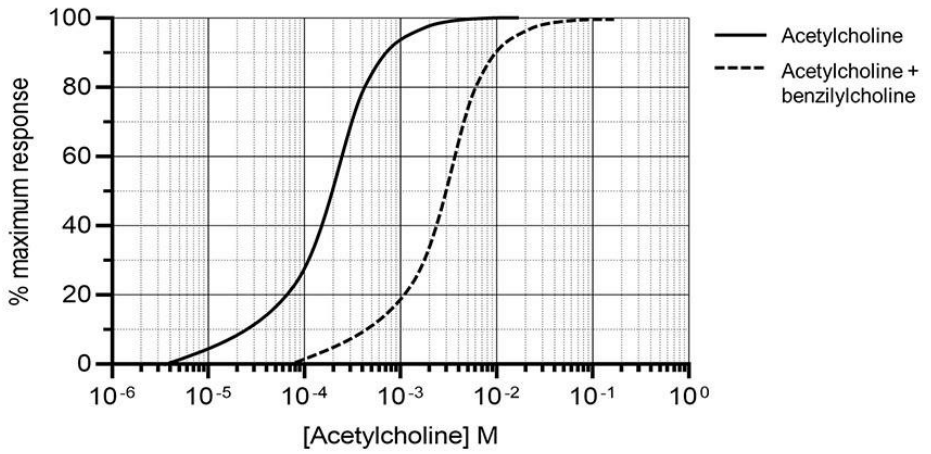
Overall, it is clear that students learning is enhanced through a combination of in-person practical classes using live animal tissue and online practical classes.

How will the learning outcomes be assessed?

MedST/VetST 1B Mechanisms of Drug Action.

Section I is a written paper that lasts 90 minutes. Each question is compulsory. Section I covers the whole course in a Single Best Answer (SBA) format. Each question in Section I carries the same mark (with no negative marking). Questions often involve deriving information from graphs like those generated in practical classes (the example below is the precise same experiment students conduct in the "Affinity Constant" practical class):

1. The contractions of a section of guinea pig ileum were measured in response to acetylcholine in the absence (solid line) and presence (dotted line) of the muscarinic cholinergic receptor antagonist benzilylcholine applied at a concentration of 5×10^{-6} M. These data were plotted in the accompanying graph.



Graph shows the contraction of guinea pig ileum (as % maximum response to acetylcholine alone) plotted against the concentration of acetylcholine (M) on a log scale. The solid line shows the contractions in response to acetylcholine alone. The dotted line shows the contractions in response to acetylcholine plus benzilylcholine.

What is the dissociation constant (K_d) for benzilylcholine?

a) 3.6×10^{7} M
b) 3.6×10^{6} M
c) 3.6×10^{6} M^{-1}
d) 3.6×10^{-6} M
e) 3.6×10^{-7} M

A second example of a question demonstrating how experimental with animal tissue is beneficial is as follows:

During a summer internship project, students were investigating the function of with novel compounds developed in the Department of Pharmacology for the treatment type 2 diabetes mellitus. In one experiment, they observed that animals dosed with compound A100 excreted increased amounts of glucose in their urine.

Which of the following best describes a likely mode of action for A100?

a) Inhibition of ATP-sensitive K^+-channels (K_{ATP})
b) Inhibition of cholecystokinin receptor 2 (CCK_2)
c) Inhibition of dipeptidyl peptidase-4
d) Inhibition of glucose transporter 5 (GLUT5)
e) Inhibition of sodium-glucose co-transporter 2 (SGLT2)

Section II is a two-hour written practical examination. It consists of two questions and assesses ability in data handing, numerical manipulation, and logical reasoning, often linked to the types of experiments and equations used in practical classes. Questions may be drawn from any part of the course and will include questions on quantification of receptor-ligand interactions and pharmacokinetics. Each question

carries the same mark. (An example paper can be provided if necessary with an explanation of how it links directly to the practicals conducted by students).

Section III is a two-hour written paper. Candidates are provided with a choice of essay questions and are required to answer three. Each question in Section III carries the same mark.

NST 1B Pharmacology.

Paper 1 will last three hours. There will be 6 compulsory questions that have a choice of 2. These require extended answers in the form of bullet points, figures and written text. Each question will carry the same mark.

Paper 2 will be a three-hour written practical examination. It will consist of two questions and will assess ability in data handing, numerical manipulation, and logical reasoning. Questions may be drawn from any part of the course and will include questions on quantification of receptor-ligand interactions and pharmacokinetics. Each question ends with an extended answers related to receptor-ligand interactions and pharmacokinetics respectfully. Each question will carry the same mark.

As with MoDA Section 2, Paper 2 for NSTIB Pharmacology is often linked to the types of experiments and equations used in practical classes.

The use of animals in teaching must be comprehensively evaluated. This evaluation should take into account the ethical considerations and all welfare aspects of animal use associated with teaching, and the implementation of the principles of replacement, reduction and refinement (the 3Rs) in all such work.

Replacement

- **Have you investigated methods to replace the use of animals?**

Yes

- **List all the replacement methods have you considered.**

Simulation software, fluorescent techniques and virtual practicals.

The number of animals we use has been reduced considerably since 2011.

In 2011, we implemented the use of SimHeart, a simulation software that we currently use to run our Lagendorff practical for both NST 1B and Med/VetST 1B courses. Thanks to this, we managed to reduce the use of Guinea-pigs from 206 animals annually (until 2011) to 57 annually (between 2015 and 2019). **This represented an annual reduction in the use of animals of 72.3%.**

In addition, in 2019/20, we updated our NST 1B MiniProject program in Lent Tern and eliminated the use of rats, reducing the total number of animals from 12 to 6 (50% reduction) for the Miniprojects.

Miniprojects were reviewed again in 2020-21 and substituted by drug review projects which do not require the use of animal tissue. Drug review projects have been delivered since then.

Furthermore, in 2020/21, we merged and rescheduled our traditional MoDA practicals, Extended Investigation and Unknown Drugs, into one single practical, which have reduced the used of Guinea-Pigs by 50%, from 16 to 8 animals for this practical.

In 2022/23 we removed the Chick Biventer and Finkelman practical classes, thus eliminating the use of chickens and rabbits respectively. **This represents a further reduction of 22 animals (35.5% reduction) in the total number of animals used.**

In 2022/23, we also eliminated the use of guinea pigs (2 animals) in our NST IB Langendorff demonstration as this practical was delivered online and will continue an online practical in 2023/24.

Summarising, since 2011 we have reduce the use of animals for teaching as follow:

Guinea-pigs: 80.6% reduction
Rats: 100% reduction
Chickens: 100% reduction
Rabbits: 100% reduction

We continue investigating alternatives to reduce the use of animals further.

- **If these methods could not be implemented, please provide the reasons (i.e. the limitations of the methods)**

Reduction (Please provide the teaching schedule as an Annex to this form)

- **Where will you source the animal(s)?**

Suppliers:
Guinea-pigs from B&K when not possible to obtain animals from other source.

A provisional teaching schedule is attached.

- **Could your work be undertaken using surplus stock animals and if so, have you attempted to access surplus stock animals: Yes/ No**

Yes, if available, but some serious limitations exist as we experienced in 2022-23*.

- **If you have answered 'No', please explain why:**

The tissue we use needs to be fresh and used immediately after dissection, otherwise it will not work.

*In 2022-23 we managed to acquire animals from the Heeney group, which were maintained after their vaccine protocol finished. Unfortunately, we experienced some issues related to the tissue response to our treatment in the practical classes.

The tissue from 15 out of 40 guinea pigs used did not work as anticipated based upon our extensive experience with this preparation. This had not happened in previous years and we think is likely due to the age and/or treatment the animals had been exposed to, the animals being far older than the animals we routinely use for this purpose.

This approach of using older/vaccinated animals also resulted in negative feedback from students, which we have not previously encountered:

"Regarding the practical, many of the guinea pig ileums used did not work, despite numerous tries, meaning that many people ended up joining other groups halfway through the practical. As a result, people felt it was a very long time to spend on a practical with little gain, especially since it also took a while to set up the guinea pig ileum."

Despite this issue, we were willing to use animals from Heeney group again this year. However, following discussion, they are unable to provide animals in the academic year 2023-24. Further exploratory emails have also not yielded any positive answers.

Due to the number of guinea pigs required on specific dates, it is very unlikely we will find another alternative source of animals and, as approved last year, we request to purchase animals from a commercial supplier.

- **If you have answered 'Yes', which UBS biofacilities have you approached:**

The Heeney group and CAF.

- **If you are proposing to use animals which are currently under Project Licence authority, please give the Project Licence details and why you propose using these animals:**

n/a

- **Will some of the tissues/organs from the animals used in this teaching programme be used in another teaching or research programme? If yes, please provide details:**

We always try to find other departments or groups that can potentially benefit from the parts of the animal we don't need. For example, we have collaborated with the following people:

Dr David Bulmer. Department of Pharmacology. Guinea-pig small intestines.

Julia Becker (PhD student). Anatomy. Guinea-pig spinal cords.

Prof. Ewan Smith will be taking guinea pig dorsal root ganglion samples in the coming year.

Refinement

- **Please give details of the accommodation in which the animal(s) will be kept:**

University of Cambridge:
Guinea-pigs: CAF

- **Will your animals be individually or group housed (if applicable). If individually, why is this necessary, and how long will your animals be individually housed?**

They will be group housed.

- **If applicable, how will your animals be identified?**

n/a

- **If animals are to be cared for by individuals, other than Animal Technicians employed by the University, please give details (*e.g. qualifications and experience of the non-UBS staff/students who will care for the animals*):**

n/a

- **What additional refinements you are planning to implement?**

Once animals have been moved from the animal facilities to the teaching lab, they remain in the designated area under very quiet conditions (avoiding noises and the access of people that can stress the animals) until the start of Schedule 1. Animals are always kept together.

Please describe precisely the Schedule 1 method you intend to use and the secondary method which must be taken to ensure the animal is dead. Guidance on the operation of ASPA (Page 125-126)

Killing a protected animal for a scientific purpose at a designated establishment does not require a licence if a method listed in Schedule 1 is used. However, all personnel carrying out Schedule 1 methods must be included on the University of Cambridge Euthanasia Register. If the method of killing to be used is not on Schedule 1, the killing method is a regulated procedure and will require personal and project licence authority.

Guinea-pigs (< 500gms): Sedative (isoflurane) appropriate for size of species, followed by dislocation of the neck and exsanguination by decapitation.

Guinea-pigs (> 500gms): Exposure to isoflurane following of overdose of injectable anesthetic via intraperitoneal route, wait until the animals has stopped breathing and heart the has stopped beating to confirm death and followed by exsanguination by cutting the femoral artery.

Please note that animals not subject to the Animals (Scientific Procedures) Act 1986, may be subject to the Protection of Animals Act 1911 and Animal Welfare Act 2006. You may be required to produce relevant authorities and or licences.

If not humanely killed, what will happen to the animals at the termination of the project?

This is a terminal procedure.

Expected duration of the project (Please note for projects or requests for materials that extend beyond 12 months a new non-regulated teaching application will be required every 12 months).
In relation to this teaching programme, please provide the planned start and end date.
Start date: October 2023

End date: March 2024

Signature of Applicant: Sergio Tomey / Ewan Smith_ Date:___12/06/2023__

Signature of NACWO: _____ Date: _____

Signature of NVS: _____ Date: _____

Signature of Chairperson: _____ Date: _____
of the UBS AWERB Committee

Please return this completed form to the Named Animal Care and Welfare Officer (NACWO) for your Department who will present the application through the AWERB Process.

Please do not arrange to start work or source materials from animals until you have received this form countersigned by the UBS AWERB Chairperson or designated deputy.

Annex 1. Provisional teaching schedule:

Animals 2023-24.

Animal Use. Teaching Lab.			Species
DATE (provisional)	**PRACTICAL**	**Course**	**Guinea pig**
06/10/2023	Affinity Constant	MoDA	1
09/10/2023	Affinity Constant	MoDA	1
13/10/2023	Affinity Constant	MoDA	1
16/10/2023	Affinity Constant	MoDA	1
17/10/2023	Affinity Constant	NST 1B	1
18/10/2023	Affinity Constant	NST 1B	1
20/10/2023	Affinity Constant	MoDA	1
23/10/2023	Affinity Constant	MoDA	1
28/10/2023	Affinity Constant	MoDA	1
30/10/2023	Affinity Constant	MoDA	1
03/11/2023	Transmural/Langendorff 1	MoDA	2
06/11/2023	Transmural/Langendorff 1	MoDA	2
10/11/2023	Transmural/Langendorff 2	MoDA	2
13/11/2023	Transmural/Langendorff 2	MoDA	2
17/11/2023	Transmural/Langendorff 3	MoDA	2
20/11/2023	Transmural/Langendorff 3	MoDA	2
21/11/2023	Trunsmural	NST 1B	2
22/11/2023	Trunsmural	NST 1B	2
24/11/2023	Transmural/Langendorff 4	MoDA	2
27/11/2023	Transmural/Langendorff 4	MoDA	2
Lent term			
02/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
05/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
09/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
12/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
16/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
19/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
23/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
26/02/2024	Ext. Inv. Unknown Drugs	MoDA	1
05/03/2024	Ext. Inv. Unknown Drugs	NST 1B	1
06/03/2024	Ext. Inv. Unknown Drugs	NST 1B	1
Totals			**40**