

Primate Welfare Meeting

25 November 2008

Breeding and Supply



Agenda – NC3Rs Primate Welfare Meeting 2008

09.30 – 10.00 REGISTRATION and COFFEE

10.00 – 10.10 WELCOME and INTRODUCTION

Mrs Sarah Wolfensohn, University of Oxford

ANIMAL WELFARE

10.10 – 10.35 Importance of the rearing environment on behaviour and physiology – implications for subsequent welfare and science

Professor Hannah Buchanan-Smith, University of Stirling

10.35 – 11.00 The role of animal welfare in the supply of macaques and its impact on research

Dr Moshe Bushmitz, BFC Israel Ltd. & Dr Corri Waitt, University of Oxford

11.00 – 11.25 Animal welfare in breeding colony quality management systems – SOPs and accreditation

Mrs Mary-Ann Griffiths, Bioculture Mauritius Ltd.

11.25 – 11.50 COFFEE

GENETIC AND COLONY MANAGEMENT

11.50 – 12.15 Genetic management of captive colonies of non-human primates bred for biomedical research – why and how?

Dr David Smith, University of California Davis

12.15 – 12.40 Observed differences in MHC genotype in macaques and implications for studies on infectious diseases

Anon, Centre for Emergency Preparedness and Response, Health Protection Agency & Anon, National Institute for Biological Standards and Control

12.40 – 13.05 Colony management – customer needs: an update from CFM

Dr Malcolm Gamble, Centre for Macaques

13.05 – 14.25 LUNCH

STRATEGIC ISSUES

14.25 – 14.50 Harmonisation of standards internationally and the ILAR Guide

Dr Joseph Kemnitz, Wisconsin National Primate Research Center

14.50 – 15.15 How AAALAC handles different standards internationally

Dr Christian Newcomer, AAALAC International

15.15 – 15.40 Home Office system for the acceptance of overseas primate suppliers to the UK

Mr David Buist, Animals (Scientific Procedures) Inspectorate, Home Office

15.40 – 16.05 UK import and transport issues – the business perspective

Anon

16.05 – 16.30 DISCUSSION and CLOSE

Mrs Sarah Wolfensohn, University of Oxford

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Importance of the rearing environment on behaviour and physiology – implications for subsequent welfare and science

Professor Hannah Buchanan-Smith, University of Stirling

Both within, and between species, there is extensive variation in natural rearing experiences of wild primates in relation to their social and physical environments. For example, parenting styles, social interactions and the availability and predictability of food will affect behavioural development and physiology. Similarly, within facilities which breed primates for laboratory experimentation and testing, there is a range of different rearing practices, and the early life experience of the animals will have a critical impact on their responses to subsequent husbandry practices and testing protocols, and on the scientific output. This presentation will review studies which have investigated the early rearing environment of primates, focussing on the implications for both welfare and science.

The influence of the rearing environment commences before birth; prenatal stress involving maternal psychological disturbance affects the hormonal and behavioural development of the offspring. Postnatally, an appropriate early social environment is vital to produce well-adjusted animals which make valid models for biomedical research. Maternal separation studies have shown severe detrimental effects on: behaviour and temperament (e.g. stereotypical and self injurious behaviours, depression, ability to cope with adversity); reward sensitivity and motivation; physiology, stress reactivity and immune function. The physical environment, including the quantity of enrichment provided and the primate's perception of control, is also known to impact development and behaviour. Macaque males show a higher predisposition to certain effects than females do.

Therefore early environments have the potential to have marked influences on primate use in the laboratory. Rearing experience (e.g. mother, nursery or pair-rearing, rotational hand-rearing, etc.), weaning age, and socialisation to humans are very different across breeding facilities and the impact of the variation on the subsequent husbandry of the primates and scientific output is rarely investigated. However, early life stress and separation may affect the ability to form good social relationships, which will influence welfare through stability of group housing; early life experiences may influence how well primates respond to transport and adapt to new environments; early interactions and responses to humans will have implications for subsequent husbandry and handling (e.g. positive reinforcement training); and anhedonia (i.e. reduced reward sensitivity and motivation) will impact on cognitive research tests and procedures for getting animals to work (fluid and food management etc.). In order to reduce the numbers of primates used for biomedical research, and for those used to be valid models, more research is required on identifying the most beneficial rearing practices, investigating if there are any sensitive periods where stress should be avoided, and how to buffer adverse effects associated with the captive environment. Collaboration between breeding facilities and the laboratories where the primates are used is required to ensure the primates are being reared in ways which are the most beneficial for subsequent welfare and laboratory use.

The role of animal welfare in the supply of macaques and its impact on research

Dr Moshe Bushmitz, BFC Israel Ltd. & Dr Corri Waitt, University of Oxford

Currently, there is a huge disparity in the breeding and rearing conditions for primates imported into the UK for research. Breeding facilities vary greatly in terms of the physical environment provided, feeding and nutrition, social management, weaning policies, environmental enrichment and transportation procedures, as well as in the use of SOPs and protocols relating to animal welfare. These differences have implications both for animal welfare and for the suitability of these animals as research models. This talk will address the issue of macaque welfare and supply by discussing how to meet the behavioural and physical needs of breeding macaques and their offspring, as well as the importance of investing in welfare. The implications of not considering welfare in supply selection criteria will also be discussed. It is essential to raise awareness amongst researchers about the importance of welfare during breeding and rearing and about the existing conditions of facilities that supply macaques for research. Finally, we suggest that supervisory authorities implement a welfare grading system that would be equivalent to current assessments of health status, taking into account important indicators of welfare. By implementing a welfare grading and welfare management system, this would reward those facilities that invest and commit to the wellbeing of the animals they maintain, and could raise the standards amongst those facilities where welfare has not been prioritised. This would also provide the end user with the ability to make informed decisions based on the quality of the breeding and rearing environment when choosing where to source animals from.

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Animal welfare in breeding colony quality management systems – SOPs and accreditation

Mrs Mary-Ann Griffiths, Bioculture Mauritius Ltd.

Bioculture Mauritius Ltd., established in 1984, pioneered the monkey (*Macaca fascicularis*) breeding industry in Mauritius, where naturally occurring B-Virus free macaques were introduced in the 17th century from Java.

Bioculture's operations are based on maximising animal welfare while ensuring the supply of top-quality research subjects to the UK and USA markets. High welfare standards form an integral part of Bioculture's ISO-certified and AAALAC-accredited Quality System.

High welfare and general good breeding colony management standards should be taken into account as part of the UK Home Office system of acceptance of overseas suppliers, and must be an important consideration for companies operating to GLP and AAALAC standards when choosing their source of primates for research.

Bioculture also believes that maintaining high standards of animal welfare and quality are fully compatible with the running of a financially viable and efficient company in an increasingly competitive global market place.

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Genetic management of captive colonies of non-human primates bred for biomedical research – why and how?

Dr David Smith, University of California, Davis

Their close genetic relationship with humans makes non-human primates more useful in biomedical research, particularly that focused on infectious diseases, than taxa, such as rodents or other mammals, that are more remotely related to humans. When highly inbred lineages of research subjects are unavailable for biomedical research on the animal species of choice, highly genetically homogeneous lineages of non-human primates, such as Mauritian long-tailed macaques or Japanese macaques, can minimize confounding inter-animal genetic influences on phenotypic variation in disease susceptibility and resistance, such as that at the MHC region. Alternatively, maximizing genetic heterogeneity WITHIN captive colonies and minimizing genetic differences AMONG captive colonies simultaneously: 1) optimizes opportunities to detect novel animal models for particular diseases and reduces loss of fitness due to inbreeding; and 2) minimizes the proportion of phenotypic variance in traits of biomedical importance that is due to genetic differences among subjects of research, minimizing the sample size of research subjects.

Estimates of gene diversity, or H , and genetic subdivision, G_{ST} , provide measures of genetic diversity within and among colonies, respectively, and should be monitored as part of the genetic management of captive colonies. Genetic markers used to estimate these two parameters can also be used to construct pedigrees using parentage analysis and to conduct studies of linkage and association of candidate genes, or known locations in the genome, with particular diseases. While microsatellite (STR) loci that exhibit a large number of alleles per locus have been used for genetic management, their density in the genome is far too low for use in whole genome studies of linkage and association. For this reason, single nucleotide polymorphisms (SNPs) are being identified by re-sequencing in several non-human primate species whose genomes have been sequenced and confirmed by genotyping a representative sample of the species. Whole genome association studies will require genotyping tens of thousands of SNPs evenly distributed across the genome using high throughput genotyping platforms and specialized bioinformatics tools for analysis. The National Institutes of Health in the US has begun to develop such resources for analysis of the rhesus macaque genome.

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Observed differences in MHC genotype in macaques and implications for studies on infectious diseases

Anon, Centre for Emergency Preparedness and Response, Health Protection Agency & Anon, National Institute for Biological Standards and Control

In studies using macaque models of TB we at the Centre for Emergency Preparedness and Response have observed differences in susceptibility between rhesus macaques and cynomolgus macaques of different origins. Further analysis has shown distinct differences in terms of innate white cell populations and in immune responses to infection.

The National Institute for Biological Standards and Control will present data on the MHC characterisation of cynomolgus macaques housed at the Porton Down facility, and demonstrate how this information is enabling us to establish a genetics-led breeding programme. We are performing association studies with the MHC genotype of cynomolgus macaques used in SIV vaccination studies to better understand correlates of protection.

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Colony management – customer needs: an update from CFM

Dr Malcolm Gamble, Centre for Macaques

The Centre for Macaques (CFM) breeds and supplies rhesus macaques for use in academic research within the UK. Tissues and organs are also supplied when available. Researchers funded by the Medical Research Council, Biotechnology and Biological Sciences Research Council and Wellcome Trust are required to obtain their animals from the Centre.

The CFM is centrally placed to explore animal breeding, training and habituation methodologies, to liaise with users in providing animals fit for purpose, and to rationalise future stock requirements. Training and guidance programmes can also be provided for visiting animal technicians and researchers to facilitate the dissemination of current best practice.

An update will be given of the development of matrilineal breeding groups to increase the productivity of the colony, and how closer liaison with research groups has enabled bespoke training and habituation regimes to be established within allocated groups of animals. The purchase of a sophisticated computerised colony management system and the refurbishment of the stock areas to allow researchers greater access to their animals prior to issue will also be reviewed.

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Harmonisation of standards internationally and the ILAR Guide

Dr Joseph Kemnitz, Wisconsin National Primate Research Center

The use of nonhuman primates (NHP) in research has resulted in discoveries that have led to significant improvements in human health and quality of life, and there will be a continuing need for using NHP in medical research for the foreseeable future. As awareness and sensitivity regarding the appropriate care and use of NHP is increasing internationally, various governments, professional organizations and interest groups have produced guidelines for the use of NHP. Attempts to formulate best practices and to establish standards of care are complicated by the variability in needs for particular species and by changes in these needs across phases of the lifespan. These attempts are further complicated by societal and institutional differences and by historical precedent and local practices. Given the increasing globalisation of research collaboration and the need for NHP in biomedical studies, it is important that guidelines do not conflict internationally. The *Guide for the Care and Use of Laboratory Animals*, developed by the Institute for Laboratory Animal Research (ILAR) and currently undergoing revision, is widely used around the world to assist institutions in caring for and using NHP and other animals in ways that are scientifically, technically and humanely appropriate. ILAR is also pursuing the development of an International Primate Plan that will address issues such as supply, conservation and transportation of NHP. These documents are meant to reflect sound information and to be consonant with the aspirations of the international community regarding NHP in research.

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How AAALAC handles different standards internationally

Dr Christian Newcomer, AAALAC International

AAALAC International conducts a voluntary, confidential, peer-review process to assess and accredit animal care and use programs involving the use of vertebrates in research, testing, teaching and production activities. More than 760 programs located in 29 countries are now participating in AAALAC International's accreditation program. Several hundred of the accredited programs conduct research activities using non-human primates, and many are involved in breeding non-human primates for internal research use or as a commercial supplier.

Now in the midst of its 5th decade in operation, AAALAC International has adapted and refined its review processes to ensure institutions have appropriate research oversight mechanisms; sound provisions for animal management, veterinary care and personnel training, education and protection; and well-maintained facilities that provide for the security, comfort and stability of research animal models. AAALAC's review is primarily grounded in the *Guide for the Care and Use of Laboratory Animals* (Guide) and supplemented by other authoritative reference documents as well as in expert professional judgment. AAALAC's approach to programmatic review and evaluation generally emphasizes the use of science-based performance standards rather than the more prescriptive engineering standards. However, AAALAC recognizes and applies the laws and guidance documents that are nationally or regionally-based, and these may supplant the Guide as the primary reference when they result in an equally satisfactory performance outcomes. The ability of AAALAC's peer-review process to draw upon diverse reference documents in addition to the Guide, and to incorporate information on best practices from the current literature, helps ensure a highly relevant and rigorous review while affording institutions ample latitude in the design and implementation of quality animal care and use programs.

Several examples will be offered to illustrate the nature of AAALAC's peer review program as it applies to organizations breeding and supplying non-human primates, and the role played by AAALAC's professional experts with non-human primate expertise in the evaluation and the final determination of the organization's accreditation status.

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Home Office system for the acceptance of overseas primate suppliers to the UK

Mr David Buist, Animals (Scientific Procedures) Inspectorate, Home Office

In the UK the acquisition of non-human primates from overseas sources for research purposes is subject to additional controls to ensure that the Home Office is aware in advance of all importation of primates by designated establishments. Each consignment of animals from an overseas source requires prior approval which is given only if the conditions at the breeding centre are acceptable to the Home Office. Following each acquisition the Home Office is supplied with information relating to the health and welfare of the animals. While the Home Office has no jurisdiction to approve or accredit overseas breeding centres, it would not approve a request to acquire and use non-human primates from a centre that had not been appraised and deemed acceptable. The criteria on which appraisal of overseas breeding centres is based sets compliance with the Home Office *Code of Practice for the Housing and Care of Animals in Designated Breeding and Supplying Establishments* as a guiding principle and identifies qualifying standards of housing, husbandry and care, pre-export conditioning, transport, breeding management, including minimum weaning age, and record keeping. Details of breeding centres are submitted to the Home Office in a standardised format and scrutinised by the Inspectorate. In most cases, overseas centres are visited periodically by the Inspectorate to gain additional information on animal care and management of the facility. Where a centre's continued acceptability is being reviewed, account is also taken of reports submitted by users following receipt of previous consignments. Where appraisal of a centre by the Inspectorate reveals deficiencies in the qualifying standards, or acceptance would raise issues of particular concern, the Home Office will seek additional advice from the Animal Procedures Committee. Once an overseas centre is deemed acceptable, its status will be subject to periodic review, typically every 2 years.

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UK import and transport issues – the business perspective

Anon

1. *“If we can’t get animals into the UK, then there is no biomedical R&D in the UK as the bulk of our work, at some point, requires the use of animals to progress.” (Recent quote from a senior executive in an international pharmaceutical company that is based in the UK)*

This seems a commonly held belief, but how true is it?

2. *“No primates – no work.” (Recent quote from a senior executive of a UK based CRO)*

This is undoubtedly true, but what follows?

3. *“Our aim is to bring about an end to the transport of animals to vivisection laboratories from the airports and ferry ports of Britain, whether guinea pigs from Newchurch being flown out to labs around the world from Manchester, to the primates coming through Dover and Heathrow: this vicious trade will be stopped.” (Statement on animal rights website)*

How credible is this threat and what are the consequences?

4. *“Any animal used or intended for use in a procedure shall be provided with accommodation, an environment, at least a minimum degree of freedom of movement, food, water and care, appropriate to its health and well-being. Any restriction on the extent to which an animal can satisfy its physiological and ethological needs shall be limited as far as practicable.”*

“The well-being and state of health of animals shall be observed sufficiently closely and frequently to prevent pain or avoidable suffering, distress or lasting harm.”

(ETS 123: European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. Strasbourg, 18.III.1986)

How is this being translated into a reality?