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In Focus

Center of Comparative Medicine & Pathology
Research Animal Resource Center
Laboratory of Comparative Pathology

Reporting on Animal Models in Scientific Publications

The provision of clear and thorough methods in publications using animal models is critical as it enables researchers to interpret the data, evaluate and replicate findings, ensure ethical animal use, and ultimately advance science.[1] To promote the inclusion of sufficient information in publications on animal studies, the National Research Council's Institute for Laboratory Animal Research (ILAR) appointed a committee of experts in laboratory animal research and scientific publishing to provide guidance to journal editors, authors, and reviewers on the topic. To execute its task, the committee conducted an extensive literature review on this topic.

Appropriate reporting when utilizing animals in animal research includes providing a complete description of: 1) the research animal (e.g., age, sex, weight, and life stage, source, genetic nomenclature, microbial/pathogen status, group assignment, and animal preparation such as quarantine, acclimation, training, surgery, groups); 2) the animal's environment (e.g., the micro- and macro-environment, diet, water, and housing); 3) methods used, including aspects of animal care and use that can affect research outcomes (e.g., experimental effects, administration of substances, randomization methods, diet, use and/or presence of infectious agents, sample acquisition, and euthanasia methods)[1,3].

In general, the information should be sufficient to: 1) enable the reader to effectively interpret and evaluate the work; 2) ensure that others can replicate the experiments described; and, 3) identify refinement and reduction measures. The following information should minimally be included in the description:

1) **Genus and species**

2) **Sex**: Sex influences numerous biological outcomes. For studies with mixed sex groups, an explanation of the composition and numbers and how subjects are assigned to the groups.

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Inside~

Highly Immunodeficient Mouse Models – State of the Art

The need for "humanized" animal models that increase the translatability of studies has been accomplished in many cases by the development of highly immunocompromised mice strains. The NOG (NOD.Cg-*Prkdc*^{scid} Il2rg$^{tm\ 1Sug}$/JicTac) mouse, developed in 2000 by Mamoru Ito at the Central Institute of Experimental Animals (CIEA) in Japan, is one of the earliest highly immune-deficient mouse models developed for biomedical research.[5,7] Taconic Biosciences received this mouse strain in 2006, where the line was rederived through embryo transfer.[7] This immunodeficient strain was developed first by backcrossing the *Prkdc*^{scid} mutation found in a C.B-17 congenic mouse population (lacks functional T and B lymphocytes) onto the NOD/ShiJic strain (defects in antigen presentation, T lymphocyte repertoire, NK cell function, macrophage cytokine production, wound healing, and C5 complement) at CIEA for eight generations to produce the NOD/ShiJic-*Prkdc*^{scid}line.[7,9] Subsequently, the C57BL/6JJic-Il2rg line (deficiencies in cytokine signaling and failure of clonal lymphocyte expansion) was backcrossed to the NOD/ShiJic-*Prkdc*^{scid} line for a total of eight generations to produce the CIEA NOG mouse we know today.[7,8] Because of its various mutations, this mouse model lacks functional T, B, and NK cells, has dysfunctional macrophages and dendritic cells, displays reduced complement activity, and displays no leakiness of T and B cells with increasing age.[10] Leakiness is defined as the ability to develop a limited number of functional T and B lymphocytes.[1]

The NSG mouse (NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ), developed by Dr. Leonard D. Shultz at the Jackson Laboratory, was created around 2004 by backcrossing the X-linked B6.129S4-*Il2rg*^{tm1Wjl}/J allele (deficiencies in cytokine signaling and failure of clonal lymphocyte expansion) into the NOD.CB17-*Prkdc*^{scid}/J (lacks C5 complement and functional T and B cells, low NK cell activity, and displays poor macrophage and dendritic cell functions)

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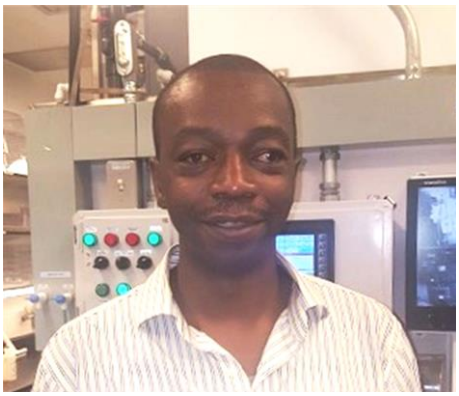
NOD.Cg-Prkdcscid Il2rgtm1Sug/JicTac (NOG) mice are the product of decades of research and the sequential intercrossing of three independent mouse strains: the NOD mouse, the scid mouse and a targeted mutation of the interleukin 2 (IL-2) receptor-γ chain (IL2rg). All of these uniquely contribute to the enhanced engraftment properties of the NOG mouse. https://www.taconic.com/taconic-insights/immunology-inflammation/origins-of-ciea-nog-mouse.html



CCMP welcomes Adedeji Afolalu, Aquatics Systems and Services Manager

The Center of Comparative Medicine and Pathology is pleased to welcome Adedeji Afolalu as the Manager for Aquatics Systems and Services.

Deji will be managing the zebrafish core facilities at both MSK and WCM. He obtained his BAgric Tech in Fisheries and Wildlife Management and has over 20 years of experience managing various aquatic species in aquaculture, public aquaria and research laboratories.

Deji joins CCMP from Rockefeller University where for 13 years he managed the Zebrafish Facility for the Laboratory of Sensory Neuroscience.

Deji's office is in Z-921 and he can be reached via email at afolalua@mskcc.org or telephone at 646-888-3478.

Image credit:https://www.upi.com/Health_News/ 2016/05/07/

Specific Pathogen Free

What's in a name?

The term SPF implies a defined health status, but the list of agents monitored can vary from colony to colony. To understand what SPF means for a specific mouse strain requires you to review the list of organisms for which that particular strain is tested.

https://www.jax.org/news-and-insights/jax-blog/2013/

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3) Internationally accepted genetic nomenclature: In addition to correct, complete genetic designations, the replicability of studies with genetically modified rodents can be supported with clear references to or descriptions of gene targeting strategies and the breeding and gene expression methods, backcross generations, substrain designation, and specific genotype of embryonic stem cells, if used. There are profound differences among laboratory rodent substrains and sources. Nomenclature guidelines are available and are reviewed and updated annually by the two international committees; current guidelines are available on the Mouse Genome Database (MGD) and Rat Genome Database (RGD) websites (www.informatics.jax.org/mgihome/nomen/index.shtml and http://rgd.mcw.edu/nomen/nomen.shtml, respectively).

4) Age and weight: Age can affect biological results including disease course, physiologic state, and response to experimental variables. Body weight is not identical to age; the correlation is highly dependent on the animal's life stage, stock, and strain. In addition, numerous husbandry, nutritional, and environmental factors influence body weight.

5)Source: Differences in environmental and microbial (e.g., gastrointestinal flora) conditions between commercial breeders and between production facilities within a commercial breeding operation can be substantial and may affect study outcomes depending on study endpoints. Thus reporting the animal's source is critically important.

6) Physiologic state and/or health status: The microbial/pathogen status of a research animal or model can influence many types of biological effects and study responses and thus affect the ability to replicate findings. There is no universal agreement about which agents are considered pathogens or which should be excluded for particular types of research or species. Ambiguity can be reduced by providing a list of the pathogens excluded or reference to the pathogen exclusion list from the commercial supplier. In addition, a description of the equipment and procedures used to maintain microbial biosecurity during the experiment can help reduce variability based on pathogen status.

Numerous aspects of the animal facility environment can affect study outcomes. The macroenvironment (conditions within the animal holding room) including temperature, humidity, lighting (e.g., light:dark cycles and intensity), room ventilation, and housing system can influence the microenvironment (conditions within the animal's cage) and therefore is important information to include in the methods section. The description of the animals' microenvironment should include:

1) Diet: type, source, supplements, feeding method and frequency, experimental substances added (agent and dose), methods of preparation (e.g., autoclaved, irradiated, etc.)

2) Water: source, delivery method, treatment (e.g., reverse osmosis, acidification, chlorination, or sterilization)

3) Housing: physical, microbial, and social features of the animals' proximate environment including the nature of the housing (controlled environment vs. outdoor), temperature, humidity, and lighting (all with ranges); type of caging (e.g., static vs. ventilated, filtered vs. unfiltered, style, composition, dimensions); bedding and nesting materials (composition and amount); cage complexity (enrichment); housing paradigm (group vs. single); and method of cage handling (frequency and methods, e.g., aseptic transfer, methods of sterilization, etc.).

In terms of methodology, a description (in the results and/or discussion) of any significant effects of the study on the animal subjects, including clinical effects or the removal or loss of animals, should be included. It is also important to describe (dose, frequency, route, etc.) any preanesthetics, anesthetics, analgesics, or any substances administered to the animals, including those not part of the experiment (e.g., treatments for clinical conditions). Studies involving infectious agents require specific experimental detail to allow for study reproducibility including dose, pathogen strain (virulence), route of inoculation, particle size (in the case of inhalants, as it determines delivery level in the respiratory tree), vehicle, volume, and site(s) of administration. Adequate descriptions of tissue and fluid sample acquisition procedures providing specific information about the frequency, technique, equipment, site, and quantity of sampling when tissues or body fluids are obtained from research animals. Finally, a detailed description of the method of euthanasia, which can have numerous and varied effects on study endpoints depending on the methods and agents used, is also important.

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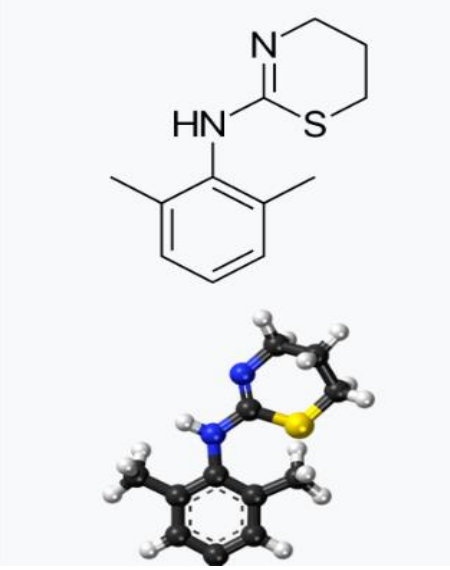
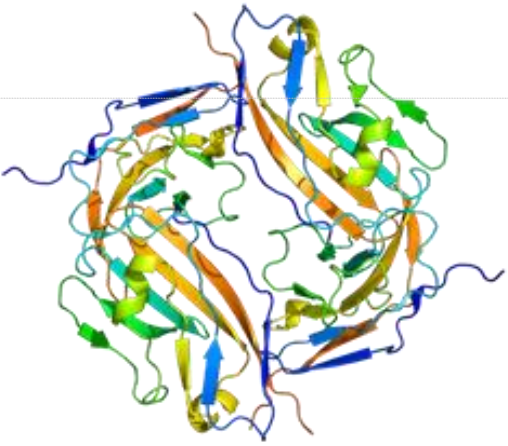


Xylazine has become a drug of abuse. Due to its hazardous side effects, including hypotension and bradycardia, xylazine was not approved by the Food and Drug Administration (FDA) for human use. As a result, xylazine's mechanism of action in humans remains unknown.

Content credit: https://en.wikipedia.org/wiki/Xylazine



Signal-regulatory protein alpha

Signal regulatory protein α (SIRPα) is a regulatory membrane glycoprotein from the SIRP family expressed mainly by myeloid cells and stem cells or neurons. SIRPα acts as an inhibitory receptor interacting with a broadly expressed transmembrane protein CD47, also called the "don´t eat me" signal. This interaction negatively controls effector function of innate immune cells such as host cell phagocytosis.

https://en.wikipedia.org/wiki/Signal-regulatory_protein_alpha

Understanding the Effects of the Anesthetics You Choose: Xylazine

Xylazine is one of the most commonly used anesthetics for surgical procedures in rodents, and justifiably so. This pharmaceutical, when used in combination with agents such as ketamine, produces reliable anesthesia in mice and rats. It also provides analgesia and muscle relaxation, which are desired when performing surgery or various other procedures. But despite its many benefits, xylazine, like most compounds, is not without side effects. And while these generally do not preclude the drug's use in research, it is important that investigators administering xylazine recognize and understand these effects as they may be problematic in specific research protocols and should not be improperly attributed to other treatments or procedures.

Xylazine belongs to a class of anesthetics and analgesics known as α2 receptor agonists. These compounds stimulate α2 adrenergic receptors throughout the body, particularly in the central and peripheral nervous system.[1] With many anesthetics, the exact mechanism resulting in the agent's anesthestic properties are unknown, but in the case of xylazine, anesthesia is largely attributable to decreased neurotransmission of dopamine and norepinephrine in the central nervous system. Other drugs in this class include clonidine, medetomidine, and dexmedetomidine. In addition to their desired effects, these drugs have the benefit of being partially reversible through administration of α2 receptor antagonists such as yohimbine or atipamezole. Although α2 agonists exert their action through the same general mechanism, each agent produces unique effects and therefore are not always interchangeable. Similarly, each produces unique side effects, which can further vary by the species to which they are administered. The specific focus of this article will be to review xylazine's side effects in mice and rats.

Certain side effects, including decreased heart rate, respiratory depression, and hypotension, are likely due to the interaction of xylazine with its target receptor, the same interaction that produces its desired anesthetic effects.[1] These effects are usually dose dependent and are also transient; they are observed only during the perianesthetic period. Once the drug has been metabolized, these side effects are no longer observed.

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Highly Immunodeficient Mouse Models,

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background for eight generations.[4,8] Although triggering through the γc chain receptor is disabled in both the NSG and NOG; the receptor is completely knocked down in the NSG, while in NOG mice the intracytoplasmic tail is truncated.[6] The NSG was originally developed to permit engraftment of human hematopoietic stem cells (HSC), but has since been used in many research applications, including xenografts, AIDs pathogenesis, and in investigating autoimmunity.[8,11] The NSG's immunologic phenotype is similar to the NOG strain, except NSG mice lack hemolytic complement and display very low leakiness of lymphocytes with age.[7,8]

Over the years, newer NSG strains have been developed to overcome limitations associated with the original NSG model. For example, the NSGS mouse (NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}Tg(CMVIL3,CSF2,KITLG)1Eav/MloySzJ) expresses human IL-3, GM-CSF, and SCF on a NSG background, allowing for superior engraftment of primary human acute myeloid leukemia (AML) samples.[10] Additionally, the NSG-HLA-A2.1 mouse (NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}Tg(HLA-A2.1)1Enge/SzJ) expresses a human HLA-A2.1 MHC class I molecule on the NSG background, making them a useful model for studying T cell responses to human viral infections, specifically Epstein-Barr virus.[10] More information on various other NSG variants can be accessed at the Jackson Laboratory's website at https://www.jax.org/jax-mice-and-services/find-and-order-jax-mice/nsg-portfolio.

More recently in 2014, the NCG (NOD CRISPR *Prkdc Il2r Gamma* or NOD-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}/NjuCrl) mouse was co-developed by the Nanjing Biomedical Research Institute of Nanjing University and Nanjing Galaxy Biopharma using sequential CRISPR editing of the *Prkdc* and *Il2rg* loci in the NOD/Nju mouse.[2] The NOD/Nju substrain also carries a polymorphism in the *Sirpa* gene[3]. *Sirpa* (Signal regulatory protein alpha) is a regulatory membrane glycoprotein that acts as an inhibitory receptor and interacts with the transmembrane protein CD47.[12] This interaction negatively controls effector function of innate immune cells, such as host cell phagocytes.[12] The polymorphism found in the NOD/Nju's macrophages allows enhanced binding to the human CD47

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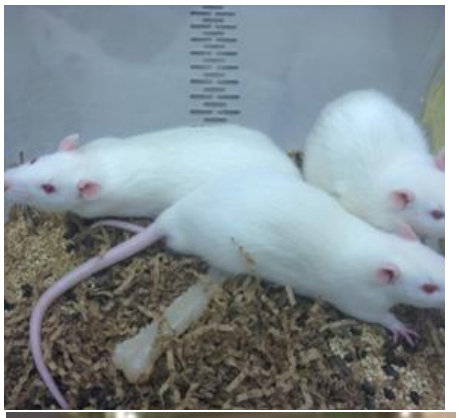

A wide variety of enrichment choices are available for laboratory rodents from nyla chew toys and nesting materials (top photo), to cage "furniture" with new products constantly under review by RARC's Enrichment Coordinator (EC). Please **DO NOT** offer any non-standard materials or cage props without consulting with the EC! Every addition must be thoroughly evaluated for species suitability and safety and approved by the Institutional Animal Care & Use Committee.

Image credit: http://www.bio-serv.com/

A New Look at Animal Enrichment and Social Housing

Enrichment and social housing are ever growing areas of focus in biomedical research using animal models, as more and more data demonstrate their value in producing high quality science. The 8th edition of the Guide for Laboratory Animal Care and Use emphasizes the need for animal care and use programs to focus on the identification and implementation of best methods for enrichment and social housing. RARC and both MSK's and WCM's IACUCs have responded to this call to action and commissioned a committee that included members from various RARC sections and the IACUC, to critically review the literature with the aim of recommending best practices for effective enrichment and social housing.

The committee recently presented their findings and their proposal for setting a standard for group-housing rodents and providing enrichment which reinforce the species' social and behavioral needs. The plan also addresses the need for additional enrichment when social housing is not possible. Additionally, the position of Enrichment Coordinator (EC) was established in support of the implementation of these important initiatives. The EC is currently conducting trials exploring the effectiveness of various enrichments paradigms. These trials include providing rats with gnawing and evaluating a variety of nesting materials for use with mice. Future activities will include a critical review of the large animal enrichment program.

~ Jeannine Carson-Rodgers

Understanding the Effects of Anesthetics Cont. from pg. 3

In addition to these effects, xylazine causes hyperglycemia in various species, including mice and rats.[2,3] Therefore, it should not be used when measuring blood glucose or in studies in which changes in blood glucose would interfere. The exact mechanism is poorly understood, but decreased insulin concentrations and insulin sensitivity have been shown to contribute. The hyperglycemia is transient but can persist at least an hour following recovery from anesthesia.[3]

Lesser known side effects in rodents include ocular lesions. Over thirty years ago, when the ketamine-xylazine cocktail was gaining popularity as an anesthetic in the laboratory, researchers noted that the combination appeared to induce cataracts in both mice and rats.[4] Lens opacities develop shortly after anesthesia, sometimes within 15 minutes, but only persist for a few hours. Further investigation revealed that these opacities were seen when using ketamine-xylazine or xylazine alone, but not with ketamine alone, making xylazine the likely culprit. Years later, another group observed ocular opacities in rats after ketamine-xylazine anesthesia, this time within the cornea rather than the lens.[5] Findings included corneal ulceration, mineralization, leukocytic infiltrates, neovascularization, and fibrosis. Analysis revealed that these lesions occurred despite adequate ocular lubrication and that lesions decreased by reversing xylazine with yohimbine. Authors recently reported a keratopathy in mice which was also characterized by mineralization but with fewer

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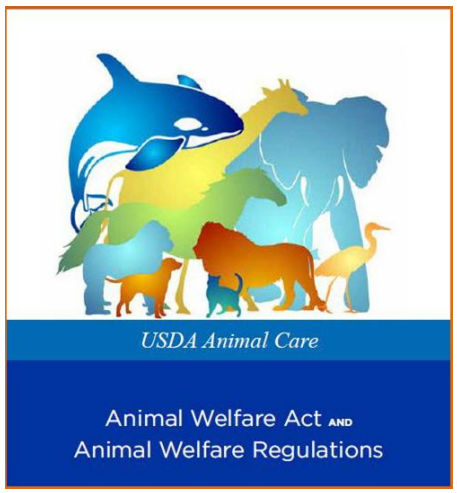
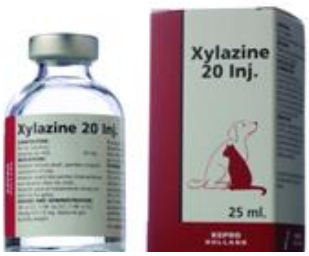
"At first I was happy I made smart transgenic mice.."



MSK's and WCM's animal care programs are subject to unannounced inspections by the United States Department of Agriculture (USDA), at least twice yearly. A major aspect of these inspections is the animal protocol review conducted by the USDA's Veterinary Medical Officer. The VMO rigorously compares what is approved in the protocol to what is observed in the vivarium. PAM is a proven way of insuring the integrity of our program and institutions.



Introducing the IACUC's In-Life Post-Approval Monitoring Program

In order to ensure the highest quality research results and prevent protocol drift, the IACUC has instituted an In-Life Post-Approval Monitoring (PAM) Program in partnership with RARC's Education & Quality Assurance (EQA) Section. The intention of In-Life PAM is to collegially review approved animal use activities as well as educate staff, share institutional policies and expectations, and meet the federal mandates for continued review of research activities related to animal use.

This program is being implemented at both MSK and WCM and all animal use protocols are considered for an In-Life PAM session. The current criteria for selecting protocols for PAM are based on a risk assessment. As examples, the use of USDA-covered species, i.e. non-human primates, constitute a high risk because of the scrutiny they receive from USDA inspectors and from the public as do rodents which undergo surgical procedures because of the potential for surgical and post-surgical complications which can negatively impact animal welfare.

Once the IACUC identifies a protocol for a PAM session, the Principal Investigator (PI) is notified by the IACUC. Subsequently, a RARC EQA Specialist will contact the PI to coordinate a date and time for the session. The PAM sessions are scheduled in conjunction with your study schedule allowing the EQA Specialist to observe the procedure and provide feedback on best practices as well as methods to avoid protocol drift.

The PAM program is another mechanism of ensuring and documenting the animal care and use program's integrity, compliance with regulations and policies, and adherence to approved animal care and use protocols. Our goal is to partner with PIs and Animal Users to meet the aforementioned goals.

~Odessa Giardino & Maureen Corby

Understanding the Effects of Anesthetics, Cont. from pg. 4

inflammatory effects.[6] In both mice and rats, these lesions were found to be irreversible. While these outcomes are uncommon, they have been reported consistently. The use of xylazine may therefore need to be avoided in certain studies involving the eye.

It is important to reiterate that these side effects do not render xylazine an unacceptable anesthetic. All anesthetics can have adverse effects, many of which are more serious or immediate than those discussed here. Nevertheless it is necessary to understand and prepare for them, and to avoid the agent when the effects will adversely alter research outcomes. As always, CCMP's veterinary staff are available to help you select the most appropriate alternatives. There are a variety of anesthetic and analgesic protocols available and these can and should be selected based on the individual project. While ketamine/xylazine cocktails are widely used and generally safe, they should not be implemented without careful scrutiny; one must think critically about the effects and side effects of each anesthetic used when planning experiments. This approach can avoid potential pitfalls and may save valuable time and resources.

~ Nicholas Tataryn, DVM

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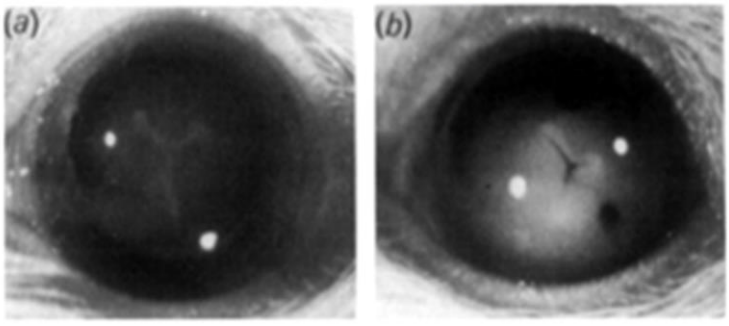

Acute reversible cataract induced by xylazine and by ketamine-xylazine anesthesia in rats and mice. Calderone L, Grimes P, Shalev M. Exp Eye Res. 1986 Apr;42(4):331-7.

The occurrence of transient lens opacities commonly seen in mice following routine anesthesia was eventually attributed to the use of xylazine. Similar lesions with corneal involvement have been identified in rats as well as other irreversible ocular pathologies in both species.

Image credit: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0132804

NOD CRISPR Prkdc Ik2r gamma (NCG) Triple-Immunodeficient Mouse

The document pictured above, NCG Mouse Information Sheet, (pdf) is provided by Charles River and can be accessed at the following site:
http://www.criver.com/files/pdfs/rms/ncg/ncg-mouse-information-sheet.aspx

Reporting the animal's macroenvironment (holding room) as well as microenvironment (cage) is equally important to understanding study results. Room air quality, stable temperature and humidity, light cycle integrity and intensity are as important as the contact bedding, species-specific feed and clean water that immediately impact the animals.

Highly Immunodeficient Mouse Models,

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ligand, contributing to efficient human cell engraftment.[12] The NCG mouse is similar to other highly-immunodeficient models, in that it is capable of hosting xenograft cells, tissues, and human immune system components.[3] The immunologic phenotype of the NCG is similar to the NSG and NOG mouse strains, except the NCG mouse has the *Sirpa* polymorphism. Additionally, NCG mice lack hemolytic complement and display no leakiness of lymphocytes with age.[3] The NCG mouse was transferred to Charles River Laboratories in 2016 from which it can now be acquired.[2]

The continued refinement of highly immunodeficient mouse models will continue to aid investigators in optimizing results in various fields, including immunological, oncological, and infectious disease research.

~ Samantha_Peneyra, DVM

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Reporting on Animal Models in Scientific Publications,

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Ensuring that all relevant information is included in a research publication is fundamental for appropriate interpretation, evaluation, and reproducibility. Failure to carefully design experiments, clearly and sufficiently describe research methods, and to correctly interpret results has negative scientific and socio-economic implications.[2] The advancement of science relies on research that is rigorous (e.g., robust and unbiased) in its experimental design, analysis, and interpretation, and reproducible in terms of findings.[5] Furthermore, it is fundamental that studies are reported in sufficient detail to allow the scientific community, research funding agencies and advocacy organizations to evaluate the reliability of research results.[4]

~ Christopher Cheleuitte-Nieves, DVM, PhD

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Hang in there and ENJOY a great summer!