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Animal Models in Genomic Research: Techniques, Applications, and Roles for Nurses

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Abstract

Animal research has been conducted by scientists for over two millennia resulting in a better understanding of human anatomy, physiology, and pathology, as well as testing of novel therapies. In the molecular genomic era, pre-clinical models represent a key tool for understanding the genomic underpinnings of health and disease and are relevant to precision medicine initiatives. Nurses contribute to improved health by collecting and translating evidence from clinically relevant pre-clinical models. Using animal models, nurses can ask questions that would not be feasible or ethical to address in humans, and establish the safety and efficacy of interventions before translating them to clinical trials. Two advantages of using pre-clinical models are reduced variability between test subjects and the opportunity for precisely controlled experimental exposures. Standardized care controls the effects of diet and environment, while the availability of inbred strains significantly reduces the confounding effects of genetic differences. Outside the laboratory, nurses can contribute to the approval and oversight of animal studies, as well as translation to clinical trials and, ultimately, patient care. This review is intended as a primer on the use of animal models to advance nursing science; specifically, the paper discusses the utility of preclinical models for studying the pathophysiologic and genomic contributors to health and disease, testing interventions, and evaluating effects of environmental exposures. Considerations specifically geared to nurse researchers are also introduced, including discussion of how to choose an appropriate model and controls, potential confounders, as well as legal and ethical concerns. Finally, roles for nurse clinicians in pre-clinical research are also highlighted.

Keywords

Genetics; Genomics; Transgenic; Nursing Science; Animal Models; Pre-Clinical

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Disclaimer About Vocabulary

This article employs some fundamental *genetics* and *genomics* vocabulary, not all of which is thoroughly defined in this text; a glossary of key terms used in this review *(italicized in the text)* is provided (Table 1). For additional clarification of terms, the reader is encouraged to utilize the freely available Glossary of Genetic Terms published by the National Human Genome Research Institute (https://www.genome.gov/glossary/). It is also important to note that "*animal model*" and "*pre-clinical model*" will be used interchangeably, though pre-clinical models also include *in vitro* techniques such as cell culture, which are not covered in this review.

Introduction and Purpose

Animal models have been an important research and teaching tool for thousands of years, and are becoming even more important in the advent of the molecular-genomic revolution. While the role of molecular genomics in nursing research and clinical practice is increasingly recognized (Anderson, Alt-White, Schaa, Boyd, & Kasper, 2015; Blix, 2014; Leach, Tonkin, Lancastle, & Kirk, 2016; Schutte, 2006; Seibert, 2014; Umberger, Holston, Hutson, & Pierce, 2013; Williams, Cashion, Shekar, & Ginsburg, 2016), the relevance of pre-clinical inquiry to nursing practice is not always readily apparent. Still, several published articles address how these areas of inquiry are germane to nurses working in both research and clinical practice (Page, 2004; Stanley & Paice, 1997; Tkacs & Thompson, 2006a; Witek-Janusek, 2004). Within the broader health science research community, a similar circumstance prevails: the role for nurses in various aspects of pre-clinical research and subsequent translation efforts is often not recognized or fully appreciated. Despite this significant gap in awareness, nurses have a rich history of contributing to pre-clinical research, including serving as: 1) members of the research team, such as principal investigator (PI), co-investigator (Co-I), or consultant; 2) overseers of pre-clinical research to ensure it meets ethical and legal standards; and 3) translators of findings to clinical trials, and ultimately, patient care. Increasing understanding of the genomic underpinnings of health and disease, which is typically rooted in pre-clinical research, enables clinicians to better treat patients via precision medicine initiatives.

The primary purpose of this paper is to address the aforementioned gap by highlighting the varied ways that nurses contribute to pre-clinical research efforts, such as study planning, approval, and conduct, as well as efforts to translate findings to clinical trials and care. A secondary aim is to provide nurse scientists interested in conducting animal research with key considerations relevant to planning and executing animal research studies; in doing so, helpful resources for further information will be highlighted. Though the secondary aim is primarily tailored to a nursing research audience, the information may also be relevant to clinicians in helping them to evaluate the quality of pre-clinical studies. To the authors' knowledge, this is the first publication to focus on a review of *animal models* specifically for nursing research and the roles for nurses engaged in, or otherwise interested in, this type of work.

The Role of Nurses

Overview of the Role of Nurses in Animal Research Historically and Contemporarily

Since antiquity, the vast majority of animal research has been conducted by physicians or bench scientists with training in a scientific discipline outside of nursing (e.g. Biochemistry; Molecular-Biology; Neuroscience; Anatomy & Physiology). Thus, in 2,500 years of documented animal research, nurses represent only a minute fraction of the scientists conducting this type of work. This can be explained partly by the comparatively new nature of the nursing profession broadly and the even newer role of nurses as scientific investigators. Given the ultimate concern of nurses is for their patients, many nurse scientists prefer to use samples drawn directly from the target population. Thus, human subjects research remains most common in the nursing research portfolio. As previously noted, though *animal models* are used in nursing, the number of nurse scientists utilizing them remains small; nonetheless, it is undeniable that the co-existence of pre-clinical research to the prevailing clinical studies within the nursing research portfolio serves to strengthen the nursing knowledge base (Witek-Janusek, 2004). Fortunately, nurses have made – and continue to make– important contributions using pre-clinical research as PIs, Co-Is, consultants, and/or collaborators on animal experiments; nurses also contribute to animal research in more indirect ways. Each of these will be discussed in detail below, followed by a selection of exemplar research applications where nurses have contributed to the pre-clinical knowledge base.

Nurse Clinicians—Nurses in clinical practice have several important roles and responsibilities in biomedical research and translation to the bedside (Sadler, Lantz, Fullerton, & Dault, 1999). Nurses often assist with early-phase clinical trials, which are informed by pre-clinical studies. They may also assist with study design, institutional review/approval, or interpretation of study findings. In clinical research nurses often assist with recruitment, delivery of the study drug, and/or data collection, either on their assigned unit or through additional voluntary or paid experiences. Nurses who specifically seek out the aforementioned opportunities are often motivated by the unique opportunity to contribute to cutting-edge research and an over-arching desire to contribute to improvement in patient outcomes. Some become involved when considering transferring to a nursing position in a research-intensive setting or when pursuing a research-focused PhD degree in nursing or another subject area. Others participate in pre-clinical research simply because it is part of the roles and responsibilities outlined by their employer (e.g. a hospital affiliated with a research-intensive university).

Beyond direct roles in conducting research, nurses also contribute to pre-clinical research indirectly. For instance, nurses in medical research promote high-quality studies that meet existing and evolving ethical and legal standards. Nurses participate on research ethics boards, study sections of grant-awarding agencies, and editorial boards for scientific journals. Nurses particularly interested in promoting laboratory animal welfare may elect to volunteer their time on a research review board such as a university Institutional Animal Care and Use Committee (IACUC). Nurses have a long-standing reputation as trustworthy professionals who, through their holistic perspective, are especially in-tune with patients'

perspectives, needs, and realities; thus, nurse scientists are uniquely well-positioned to help promote clinical relevance in pre-clinical studies and advance subsequent translation efforts (Tkacs & Thompson, 2006b). The various means by which nurse clinicians can contribute to animal research pose opportunities for their own learning and professional development, as well as leadership and service experiences that could be listed on a resume or curriculum vitae.

Nurse Scientists—The role of the nurse scientist in pre-clinical research is more apparent. Nurse scientists serve as PIs, Co-Is, collaborators, and consultants on grant applications and associated research projects. Three of the primary reasons why nurse scientists may want to participate in pre-clinical research will be briefly described. First, the unique strengths of *animal models* allow scientists to answer a number of health-science research questions in a way that would not be possible in clinical research (see “Strengths” heading for additional details). Second, participation in animal research diversifies the researcher's skills, which enables him/her to be a more thoughtful consumer of the pre-clinical knowledge base, and may lead to additional opportunities. Third, inclusion of the nursing perspective into pre-clinical research as part of a collaborative, trans-disciplinary research environment strengthens pre-clinical studies through the incorporation of nurses’ unique insights into patient needs, preferences, and experiences.

Nursing Research Applications

In addition to the nursing perspective strengthening the quality of pre-clinical research, it is also true that pre-clinical research strengthens the nursing science knowledge base (Rowsey, 2015). *Animal models* allow nurses to address research questions that would be difficult or impossible to answer via clinical research alone, as described in additional detail under “Strengths and Limitations.” For these reasons, many nurse scientists have chosen to employ *animal models* in at least part of their program of research. While the breadth of the literature is beyond the scope of this review, four key areas of inquiry that nurses have contributed to implementing *animal models* will be discussed as exemplars, namely: 1) evaluating physiology and pathophysiology; 2) studying the genomic underpinnings of health and disease; 3) testing interventions; and 4) evaluating the effects of environment on health outcomes. In each category, several exemplar studies with known nursing input will be briefly described, and the relevance of the knowledge generated for nursing science and practice highlighted.

Application 1: Evaluating Physiology and Pathophysiology—One of the earliest, and thus most well-established, applications of pre-clinical research was to explore the physiology of health and disease/injury. While much of this work has (both historically and contemporarily) been conducted by physician-researchers and other bench scientists, nurses have also made contributions to this effort. While not intended to be a comprehensive review, a few key examples of work in this area that were conducted with one or more nurses on the team (as evidenced by the author byline on resulting publications) are summarized below.

In one study, evidence of paravascular fluid circulation within the central nervous system (CNS) was identified (Rennels, Gregory, Blaumanis, Fujimoto, & Grady, 1985). In this study, researchers used microscopic examination of brain tissue harvested from cats and dogs after injection of a tracer; control over sample collection time (which ranged between two minutes and four hours after tracer injection) allowed for a temporal examination of events, which would not be ethical or feasible in humans. Although paravascular fluid circulation could not have been as definitively studied in humans, this effort has clear clinical relevance. First, it demonstrated that solutes within the cerebrospinal fluid rapidly have gain access to the extracellular space (ECS) via microvascular routes; prior to this study, this fluid exchange was erroneously thought to be solely due to diffusion. The authors also acknowledge that this work has provided avenues to limit paravascular influx of solutes (e.g. if this would result in adverse effects in the ECS) by diminishing or totally inhibiting pulsations (e.g. partial ligation of the brachiocephalic artery). A second study conducted by three of the researchers on the original study (Blaumanis, Rennels, & Grady, 1990) further enhanced our understanding of paravascular circulation. This follow-up study examined the effect of edema on previously reported paravascular transfer (Rennels et al., 1985). Cats were subjected to a cold lesion model that resulted in vasogenic edema and a tracer was injected to monitor paravascular circulation. In edematous regions, paravascular transport was greatly reduced as evidenced by sparse tracer levels in edematous regions. Since edema is characteristic of many CNS disorders including traumatic brain injury (Unterberg, Stover, Kress, & Kiening, 2004), stroke (Zheng, Chen, Zhang, & Hu, 2016), meningitis (Citton, Toldo, Calderone, Sartori, & Manara, 2009), and encephalitis (Lan et al., 2016), this line of inquiry has potentially far-reaching clinical applications.

A second exemplar of nursing literature investigating physiology/pathophysiology is the efforts to study the effects of endotoxin exposure. In this line of inquiry, rats were injected with endotoxin, a type of toxic compound derived from bacterial cell walls. This study could not be ethnically conducted in a randomized controlled trial in patients, yet such pre-clinical research has clear clinical relevance since endotoxins are well known to adversely affect humans similarly to test animals. Findings from these pre-clinical studies suggest that endotoxin exposure leads to downstream responses including endocrine signaling such as insulin release, somatostatin, lactate, and the pituitary hormones (Witek-Janusek, 1988; Yelich & Witek-Janusek, 1994). Since these studies were conducted, the relationship between endotoxin and hormones has been further validated with human subjects research conducted by non-nurses (Lira et al., 2012).

Yet another line of nursing inquiry is the examination of pathophysiological changes associated with stroke (Ritter et al., 2008, 2011) and strategies to target these changes therapeutically (Funk et al., 2003, 2013; Ruehl et al., 2002). In this context, pre-clinical models are a fundamental tool which facilitate analysis of brain tissue at specified post-stroke time points, which would only be possible in humans using less informative non-invasive methods (e.g. imaging). If researchers were to examine brain tissue after stroke in humans, the timing of tissue collection post-stroke would vary tremendously, considering patient death or need for neurosurgery (allowing access to brain tissue) could occur at any point after injury. This temporal understanding of pathophysiological changes associated with stroke has relevance to selecting the drug type and regimen. Interestingly, a nurse

researcher also published a scholarly dialogue paper in *Nursing Science Quarterly* detailing the interconnected nature of her pre-clinical mechanistic work and clinical experiences with this clinical population, followed by a discussion on the topic of nursing as a type of basic science (Ritter, 2008).

Application 2: Studying Genomic Underpinnings of Health and Disease— Unsurprisingly, in the genomic era, *animal models* are commonly used in conjunction with molecular and genomic research methods. Other studies indirectly explore the effects of *genes* by using test animals that have undergone *genome* modification in one or more ways. There are many examples of nurses who have contributed to molecular *genetic* research efforts using *animal models*. Several noteworthy examples are discussed below.

Identification of *genes* implicated in various disorders represents an important line of inquiry to which nurses have contributed. One study used a genome-wide screen in mice and identified a novel *gene* (Gan1) implicated in peripheral neuropathy associated with anti-retroviral therapy. One implication is that targeting Gan1 or its protein may obviate neuropathy for individuals taking anti-retrovirals (Dorsey et al., 2009). Moreover, *genetic* variation in the form of frameshift and nonsense mutations has been reported for Gan1 (Bomont et al., 2000; Kuhlenbäumer et al., 2002), which may be relevant to precision medicine initiatives aimed at identifying the best therapeutic regimens for patients with neuropathy. Another study harnessed the ability of researchers to non-controversially harness molecular techniques to generate mice that have had a particular *gene* removed from the *genome*, also referred to as a gene being knocked out (KO) (Dorsey et al., 2006). In this *mouse model*, KO of the TrkB.T1 receptor was associated with improved outcomes, including preservation of hippocampal neurons (Dorsey et al., 2006). A follow-up study using the same *strain* of mice found that KO of the TrkB.T1 receptor is associated with altered sleep, including increased time spent in REM sleep and reduced sleep continuity (Watson, Henson, Dorsey, & Frank, 2015). This information may prove relevant to precisely treating individuals with certain *genotypes* relevant to sleep disorders.

Gene expression alterations in the context of various conditions have also been explored by several nurse researchers. For example, expression of the FOS *gene* is induced in some infectious diseases and endotoxemia (Tkacs, Li, & Strack, 1997; Tkacs & Li, 1999). In another study, non-coma hypoglycemia in a rat model was found to be associated with decreased levels of neuropeptide Y and pro-opiomelanocortin mRNA (Tkacs, Dunn-Meynell, & Levin, 2000). The aforementioned studies may also lead to precision medicine initiatives. For example, some patients may benefit from anti-sense therapy, which would bind to over-expressed mRNA so that it cannot be translated to protein (Turner, 1997).

Another study evaluated the effects of sixty minutes of inspiratory resistance loading (vs. sham) in rats administered either dopamine or saline control on *gene expression* of twenty-seven known apoptotic proteins (Goodyear-Bruch, Jegathesan, Clancy, & Pierce, 2008). In the diaphragm, twelve of the proteins were expressed, two of which showed higher expression after inspiratory resistance loading when receiving dopamine treatment (vs. saline control). Specifically, superoxide dismutase copper zinc (SOD [CuZn]) and

proprioceptive event related potential (PERP) were elevated, suggesting dopamine reduces the apoptotic consequences of this condition (Goodyear-Bruch et al., 2008).

Application 3: Testing Interventions—Of clear relevance to nursing research and practice is identifying the safest and most effective treatments for the many disease conditions and symptoms afflicting patients. The early work in this process is traditionally rooted in *animal models* to establish basic safety and feasibility before translation to clinical trials is justified. Thus, it is no surprise that nurse scientists have contributed to *animal model* research testing interventions.

One study used a rat model exposed to various fever inducers to test the possible effects of methyl scopolamine as an anti-pyretic (Rowsey & Gordon, 2000), a best practice before exploring off-label effects experimentally in humans. In this study, methyl scopolamine (1 mg/kg) was administered intraperitoneally as a single dose. The therapeutic regimen used in this study was associated with marked reversal in the temperature elevation associated with stress (handling of the animal and switching the cage), chlorpyrifos (an organophosphate pesticide), and nocturnal cycles (Rowsey & Gordon, 2000). The same fever mechanisms were targeted by the known antipyretic sodium salicylate. This study identified a potential avenue for clinical trials and may also be relevant to identification of adverse effects regarding thermoregulation on patients taking methyl scopolamine.

Notably, it is not just novel pharmaceuticals that can be tested in pre-clinical models, but rather a diverse array of therapies. In one study (Bennetts et al., 2014), two fluid resuscitation formulations (Lactated Ringer (LR) vs. LR + ubiquinol) were tested as a means of improving outcomes of hemorrhagic shock in rats. Hemorrhagic shock was induced by removing forty percent of the total blood volume, treatment administered, and animal monitored for two hours prior to sacrifice. The heart, lungs, kidney, and diaphragm were harvested and analyzed. The main finding was that hydrogen peroxide levels and apoptotic proteins were reduced following LR + ubiquinol treatment, suggesting protective effects on oxidation and cell death (Bennetts et al., 2014).

Application 4: Evaluating the Effects of the Environment on Health Outcomes —The way environmental and lifestyle factors interact with health can also be easily studied in *animal models*. One study examined the effect of exercise on core temperature in a sample of female rats (Rowsey, Borer, & Kluger, 1993). In this study, exercise was associated with a higher body temperature both during the period of exercise as well as during rest. A second goal of this study was to identify the role, if any, of prostaglandin E in the elevated body temperature reported. To elucidate the role of prostaglandin E, sodium salicylate was injected in both exercised and sedentary rats; regardless of group, this injection was associated with a decrease in body temperature, suggesting the increase in body temperature after exercise is not prostaglandin-mediated.

A second line of inquiry evaluated another aspect of exercise, specifically how it relates to susceptibility to environmental toxins (Rowsey, Metzger, Carlson, & Gordon, 2003) and alterations in serum cytokine levels (Rowsey, Metzger, Carlson, & Gordon, 2009). This study built off the nurse-led team's past work which characterized the hypothermic and

hyperthermic changes associated with organophosphate pesticide exposure, and factors associated with tolerance to such effects (Rowsey & Gordon, 1997). Specifically, this study examined the effects of exercise training (vs. sedentary behavior) on the known thermoregulatory consequences of chlorpyrifos, which causes an immediate hypothermic response followed by a temperature spike. Following 8 weeks of exercise or sedentary behavior, rats were treated with either chlorpyrifos or a control solution administered via gavage over the course of 4 days. In the exercise group, the first dose of chlorpyrifos did not cause hypothermia (as it had with the sedentary animals). This study highlights the precise environmental control afforded by *animal models* and found that exercise reduced both the hypothermic and hyperthermic consequences of repeated chlorpyrifos exposure (Rowsey & Gordon, 1997). The follow-up study (Rowsey, Metzger, Carlson, & Gordon, 2006) further examined the effect of chronic exercise conditioning on thermoregulation following exposure to agents known to be pro-inflammatory (e.g. turpentine and lipopolysaccharide). In this study, female rats were randomized to two activity groups (exercise vs. sedentary) and engaged in the target activity level for eight weeks before being injected with turpentine, lipopolysaccharide, or a control solution. Turpentine led to a prolonged low-grade temperature that was slightly suppressed by exercise training when core temperatures were assessed during the day (not the night). In the lipopolysaccharide group, exercise training actually compounded the fever. Taken together, this evidence suggests that the effects of exercise are different depending on the exposure that leads to fever (Rowsey et al., 2006).

A final example is a study of the effects of maternal alcohol consumption on neonatal outcomes related to glucose balance (Witek-Janusek, 1986). Clearly, a true experimental study characterized by group randomization would not be ethically possible in clinical research, necessitating an *animal model*. In this study, female rats were placed on a liquid ethanol diet, an isocaloric liquid diet, or a standard chow diet beginning three weeks prior to mating and continuing throughout the pregnancy. Once the litters were born, the ethanol-exposed pups were found to have decreased levels of stored glycogen in the liver. This change in glycogen levels was associated with higher rates of hypoglycemia in the early post-natal period, especially when the pups were not fed. Notably, maternal liver glycogen stores were also decreased when a liquid ethanol diet was consumed (Witek-Janusek, 1986). This pre-clinical evidence has clinical relevance and likely contributed to the trend over the last few decades for healthcare providers to recommend restricting alcohol during pregnancy.

Considerations for Researchers

For nurse scientists interested in conducting pre-clinical research, there are numerous considerations they must address prior to and during study planning that can greatly affect the quality of the study. For many nurse scientists, formal educational training surrounding pre-clinical research design and methodologies is limited, which can complicate the planning process, particularly when more experienced collaborators are not available. Important considerations, including overall strengths and limitations of pre-clinical research, a discussion of the model selection process, a summary of common genomic modifications and their uses, as well as a discussion of environmental factors that may confound study findings are described below. This discussion will be tailored to a nurse scientist audience.

To further assist readers, a summary of available resources relevant to the planning and conducting pre-clinical research will be provided.

Strengths and Limitations of Pre-Clinical Research

Strengths—*Animal models* have numerous unique advantages allowing questions to be answered that would not be feasible, ethical, or even possible in human research. Arguably the greatest strength and most critical use of *animal models* is to garner fundamental information related to the safety of interventions and products (e.g. cosmetics) before application to humans. Another strength is the ability to collect long-term data without significant risk of sample attrition since test subjects are housed by researchers and monitored by veterinarians. Also, the shorter lifespan of animals enables a researcher to track the natural history of a disease or injury from the time of onset until death (if desired), which would be exceedingly more complicated in humans. Similarly, the ability to euthanize test animals at controlled times allows researchers to study the time course of pathophysiological changes associated with various conditions.

Another advantage of pre-clinical studies is that biological changes that underlie diseases and injury can be studied readily and directly. Consider a researcher trying to understand the effects of ischemic stroke on the functional tissue (parenchyma) of the brain. Extensively characterizing the effects of stroke on human brain tissue would only be possible post-mortem; moreover, since the time between stroke onset and death can range from seconds to years, it would be difficult to develop a clear understanding of the typical sequence of events. Without *animal models*, researchers would have to depend on indirect measures as a proxy for the state of the brain (e.g. functional magnetic resonance imaging [fMRI] or screening for serum biomarkers), which may obscure scientific understanding of the pathophysiology of various conditions. Using pre-clinical models, brain tissue is readily available and animals can be sacrificed by standardized methods for tissue processing at precisely controlled time points.

Beyond the types of questions that can be addressed in *animal models*, there are other strengths worth noting. First, animals share many similar features with humans, both biologically and behaviorally. It is very likely that if a researcher is interested in some aspect of the human experience (e.g. learning; depression; substance abuse), there exists one or more *animal models* available that is a good representation of the pathophysiology or behavior of interest, along with at least one established way to measure it. Another asset of *animal models* is that they are always improving. In recent years, *genetic* manipulations have routinely been made to the *genome* of animals; humanization efforts result in test animals that better model a clinical condition. Recently, a *mouse model* was developed that resulted in human-like albumin production; this model has implications for preclinical drug studies, since albumin is a possible drug delivery vehicle (Low & Wiles, 2016). In addition to the *genetic* manipulations possible, there are many other practical advantages, since the test animals' age, sex, diet, environment, and other factors can be more tightly controlled. Also worth noting is that while animal research presents its own set of ethical and legal considerations (described under the heading entitled "Summary of Ethical and Legal Considerations for Pre-Clinical Research"), generally there are less ethical and legal

concerns for pre-clinical research than there are for clinical trials. Ultimately, as the body of pre-clinical evidence grows additional avenues of clinical research become available. Notably, not all animal studies warrant extension to human studies; rather, critical evaluation of a large body of research is necessary. Indeed, it is clear that humans benefit in many ways from animal research; according to a poster published by the Foundation for Biomedical Research using data from the U.S. Department of Health and Human Services, the human life span has increased 20.8 years as a result of animal research and subsequent healthcare advances (Foundation for Biomedical Research, 2006).

Limitations—While *animal models* play an important role in advancing nursing research and the broader health sciences knowledge base, there are several notable limitations. First and foremost, while common *animal models* share important similarities of humans, no pre-clinical model perfectly represents all aspects of the complex human experience. Moreover, for any condition of interest, the combination of the animal used (species; strain; sex; etc.) and the method employed to induce the disease or condition of interest (assuming it does not naturally occur in the test animal) must be carefully decided upon, and a misguided choice could obscure the researchers' ability to address the research question adequately. There may be several techniques available to induce the condition of interest in the test animal, and each may mimic certain aspects of the pathophysiological and behavioral consequences while not reliably simulating others. Finally, there are some human conditions for which no *animal model* is available. For instance, rare (aka "orphan") disorders (e.g. Zechi-Ceide syndrome) may have no available *animal model* (Weizmann Institute of Sciences, 2015). However, rare conditions are also challenging to study clinically due to low population sizes and subsequently small samples, which limits study power. Advancements in the scientific knowledge base and genomic technologies mean that new models may become available.

A second broad-scale concern ironically stems from the high degree of control that inherently strengthens animal research. While exacting control helps to reduce confounding effects when collecting early evidence, the control characteristic of most animal studies is very dissimilar to what is seen in clinical research. Indeed, clinical trials and subsequent translation efforts are often complicated by the heterogeneity of clinical populations with respect to factors including, but not limited to, age, sex, *genotype*, and diet. Thus, when a drug is effective in all male mice of a narrow age range, it may not be easily translatable to a diverse clinical sample. Thus, generalizability of pre-clinical research is limited, necessitating accumulation of evidence across several studies. In response, leaders in the research community and funding agencies alike have highlighted the need to diversify samples in pre-clinical studies. Moreover, while a high degree of control is often planned in studies, there are many potential confounders that can accidentally be introduced to the study (see "Unintended Consequences and Confounders" heading). Finally, one must balance the ethical considerations of adequately vetting a therapy in pre-clinical models with the concern of prolonging pre-clinical trials to the extent that humans are not benefitting from the research.

Beyond these broad limitations, there are also several specific, practical limitations of animal research. This type of work requires special facilities (e.g. vivarium) and highly specialized equipment as well as staff trained in how to work safely and ethically with animals. Even

when best practices are strictly adhered to, there is the potential of harm or suffering to the animal. Similarly, working with animals poses an inherent risk to the researcher, including the risk of being bitten or exposed to a zoonotic illness that the test animal carries. Of additional concern is that housing, husbandry, and experimentation on animals can be quite expensive. Typically housing costs are paid per day, per cage and some animals need to be housed singly due to size or temperament (e.g. C57BL/6 mice are known to be aggressive). Still, it is notable that many pre-clinical studies are less expensive than clinical research, particularly when the cost of participant reimbursement is high or sophisticated molecular-genetic analysis is performed.

Model Selection

The most important decision when using an *animal model* is determining which model is most appropriate to meet the research goals. For example, if complex neurological functions such as memory and learning are of interest, mammals whose brains are more similar to humans are preferred over lower vertebrates and invertebrates with drastically different neurological structures. Typically, the extent of genotypic similarity to that of humans is of interest when choosing experimental models. Many animal *genomes* have been sequenced and analyzed, allowing quantitative comparison between humans and model organisms with respect to number of *nucleotides*, *chromosomes*, *genes*, and proteins. The percent of the *genome* that is *protein-coding,* extent of homology with human *genes*, or presence/absence of a human *gene* of interest (e.g. KO or *knockin* [KI]) can also be considered as part of model selection. Moreover, the *phenotype* of interest is often used to guide model selection. For instance, when evaluating the effect of an antihypertensive drug, the researchers may choose an *animal model* that is taxonomically close to humans vs. a cold-blooded or invertebrate model due to the similarity of cardiac and circulatory systems in mammals.

When certain types of common laboratory animals (e.g. mice) are used, model selection also includes deliberation between many available *strains*, each with their respective set of *substrains*; each *strain* and *substrain* has unique physiological and behavioral characteristics to consider. For instance, researchers testing anti-hypertensive drugs may select BPH/2 mice which have average blood pressures of approximately 145 mmHg, a full 25 mmHg higher than the most commonly used *strain* C57BL/6 (The Jackson Laboratory, 2013). If the researchers are interested in the effect of a *gene*, they may search for a *strain* characterized by a hallmark mutation of interest. Mice are commonly used to study alcoholism, because some *strains* (e.g. C57BL/6) show a high preference for alcohol (McClearn & Rodgers, 1961), which has been associated with specific genetic *loci* (Melo, Shendure, Pociask, & Silver, 1996). Recently, C57BL/6 mice were used to study the effects of maternal binge drinking on functional outcomes in their offspring (Wagner, Zhou, & Goodlett, 2014).

Choice of a biologically relevant model includes ensuring that the controls are appropriate. If using a *substrain* of mice derived from a commercially available *strain*, a general rule of thumb is that the main *strain* can be considered a suitable control for your *substrain* if the *substrain* has been maintained through strict inbreeding for at least five generations. It is also relevant to consider whether controls possess any histopathological or behavioral characteristics likely to confound study findings. C57BL/6 mice are prone to age-related

hearing loss starting around ten months, with subsequent degeneration of the Organ of Corti (Li & Hultcrantz, 1994); this hearing loss would confound studying functional outcomes (e.g. fear; cognition; beam walking) in old age using tests that require an auditory cue (e.g. white noise machine). Resources for appropriate selection of a model, strain, and substrain are described later (Table 2).

It is worth noting that some human health disorders may have no single model that fully represents the disease pathology. For example, for type 2 diabetes, there are several available models, each capturing one or more important aspects of the disease. Similarly, traumatic brain injury (TBI) is characterized by complex physiological and behavioral symptoms which persist chronically; however, outcomes vary widely across models, with some injury inductions producing more focal effects and others producing more diffuse effects. Researchers should carefully consider the outcomes of interest when choosing a model. It is also important that researchers report the details of the model (species; *strain*, *substrain*; vendor; etc.) in their publications; this not only enables replication of the study by independent researchers, but also facilitates comparison of study findings with those previously published in the literature.

Common Genomic Modifications

Modification (either reversible or permanent) to the *genomes* of animals has been well-established and represents a common avenue for research. Most notable are the efforts to humanize animals to further enhance the clinical relevance of pre-clinical studies. While there are many types of *genetic* manipulations in use, and commercially available *transgenic* animals, this introductory article will focus only on four common modifications: *knockout* (KO), *knockin* (KI), conditional (i.e. inducible) mutations and *gene* editing.

Researchers can use KO models to determine the role of a *gene*, gene products (i.e. protein), or the consequences of a loss-of-function mutation in a *gene* in one or both chromosomal copies (LePage & Conlon, 2006). Thus, researchers can identify the effects of a *homozygous* and/or *heterozygous* mutant *genotype(s)* on one or more histopathological or behavioral outcomes of interest. This is especially useful when the *gene* being knocked out is conserved across species and also found in humans. In some cases, especially *autosomal dominant* conditions, a *homozygous* mutant *genotype* is fatal before birth, necessitating the use of a *heterozygous* KO to accurately study the disease. In other cases, *heterozygous* KO animals are chosen because a *homozygous genotype* causes severely impaired development of the animal to the extent that it would interfere with experimental goals. Conversely, researchers may choose a KI model when the goal is to insert a *gene* at a particular *locus* within the *genome*. KI models insert *complementary deoxyribonucleic acid (cDNA)* at specific chromosomal *loci*, typically to create a novel disease model or further humanize a test animal. Researchers can also use KI animals to evaluate the role of the regulatory machinery (e.g. promoter regions, enhancer regions) that control *gene expression*.

Conditional mutations are mutant *alleles* that cause a change in *phenotype* from the normal wild-type animal only when exposed to certain environmental conditions or stimuli (e.g. a diet rich in some nutrient, high temperatures). For example, as seen in sickle cell anemia, carriers of the *genotype* may experience a change in *phenotype* that is conditionally

dependent upon environmental factors such as exposure to cold temperatures, low oxygen, or other restrictive conditions. Animals with *conditional mutations* are useful to researchers interested in studying disorders that occur later in life; such medical conditions are difficult to study using KI/KO models, since addition/deletion of genetic material often causes premature death. Conditional mutants are applied to identify crucial developmental *gene expression* events by exposing animals to restrictive conditions at various time points and observing the consequences.

In vivo gene editing represents a new horizon for animal research and, in some international research communities, clinical research. Largely, the prospects of gene editing in humans remains highly controversial (Hampton, 2016), though research is gaining momentum (Callaway, 2016). To date, the most popular method of *in vivo gene editing* remains the CRISPR-Cas system (Ledford, 2016). Despite the ethical and technical considerations surrounding human gene editing, in animal models *in vivo* gene editing is currently an area of rapid research development. For example, gene editing techniques have been used to improve outcomes of muscular dystrophy in mice (Long et al., 2016; Nelson et al., 2016). These techniques have also been used as a simple way to screen human gene loss-of-function (Bhattacharya, Marfo, Li, Lane, & Khokha, 2015).

Unintended consequences and confounders

There are several mundane aspects of experimental design that could potentially confound study findings, including housing (e.g. cage type; presence of nestlets/toys/etc.; light/dark cycle), diet (food type; quantity/access) and husbandry. At a minimum, these choices should be informed by a thorough review of the literature. Whenever possible, pilot testing should further determine the best environmental exposure selection.

It is also important to note that in many instances, total control over environmental factors is not possible. Often, studies allow test animals ad libitum (i.e. free, unlimited) access to chow and water. In these cases, it is inevitable that different test animals have different overall intake of food and/or water.

Depending on the experimental procedures, other potential confounders may be introduced. For example, when animals undergo anesthesia, the effects of the agent used on study outcomes should be considered; as an example, isoflurane is associated with neuroprotection (Statler et al., 2000, 2006). Researchers should pay careful attention to potential consequences of experimental procedures and make efforts to reduce their confounding effects.

Resources Available

Researchers should identify and utilize available resources at their institutions. Departments overseeing animal studies may offer training opportunities in research methodologies and responsible conduct of research. Research institutions may also offer other assistance such as shared animal research space, tissue banks, and pilot funding. Furthermore, researchers should carefully consider the available budget, taking into account the anticipated costs of animal acquisition, housing and husbandry, personnel, equipment and supplies. With respect to obtaining test animals, some institutions maintain colonies of one or more species. For

those who need to acquire test animals from outside the institution, there are many commercial sources. Researchers using *mouse models* can utilize the many national and international repositories outlined in the International Mouse Strain Resource (www.findmice.org), many of which are highlighted in Table 2. For other species of test animals, there are also resources available as summarized in previous publications (Mashimo & Serikawa, 2009; Matthews, Kaufman, & Gelbart, 2005; Smith, 2012). Notably, commercial suppliers of test animals often offer literature, webinars, and other guidance. Regardless of species, researchers are encouraged to learn as much about the test animal as possible.

Summary of Ethical and Legal Considerations for Pre-Clinical Research

As mentioned previously, some studies that would not be ethically acceptable or otherwise feasible in human subjects research may be possible using *animal models*. However, similar to human research, maintaining the highest ethical standards is of utmost importance when conducting animal research. Researchers working with animals should follow institutional and governmental guidelines, all relevant laws (e.g. Animal Welfare Act, 1966) as well as employ the best practices outlined in the G*uide for the Care and Use of Laboratory Animals* (National Research Council, 2010). Moreover, all experimental procedures must be approved by the Institutional Animal Care and Use Committee (IACUC) and strictly adhered to.

The effort to conduct ethical pre-clinical research includes: 1) selecting the least sentient animal possible to adequately address the research questions; 2) keeping the sample size to an absolute minimum as informed by available evidence and, when possible; and 3) conducting a power analysis. Studies should be designed to minimize pain and suffering. When experimental procedures are likely to induce appreciable pain, anesthesia or analgesia should be used, unless otherwise approved by the IACUC or other pertinent regulatory agency. At the end of the research study, animals should be humanely euthanized if warranted.

It is also worth acknowledging that there are some ethical concerns that over-use or over-reliance on animal models. For example, there is some risk in testing an intervention in animals for a prolonged period of time may delay translation and improvements in patient care. This is concerning given that translation from research to practice typically follows a lag time of 17 years (Morris, Wooding, & Grant, 2011). Moreover, for conditions with no United States Food and Drug Administration (FDA)-approved drugs (e.g. traumatic brain injury), this may mean patients remain largely hopeless. Conversely, prolonged animal studies are useful in identifying long-term complications of a therapy and reducing the adverse effects experienced by patients.

Closing Remarks

The ultimate goal of animal research in the molecular genomic era is to enhance human health and quality of life via improved understanding of disease, development of therapies, and application of novel genetic technologies. This goal is consistent with the overarching goals of nursing science, specifically to enhance understanding of unmet patient needs as

well as design, test, and translate interventions to address the problems faced by patients. Depending on the clinical population and body of research evidence available, the state of the science may be anywhere from preliminary basic science studies to translation of findings to clinical care; thus, nursing science is strengthened by a diverse research portfolio including both pre-clinical and clinical inquiry (Page, 2004; Rodgers & Anderko, 2004; Witek-Janusek, 2004). In addition to nurses' many contributions to the clinical research knowledge base, nurses have also contributed to pre-clinical research targeting a number of health conditions and symptom *phenotypes* (Bond, Heitkemper, & Bailey, 1998; Briones, Therrien, & Metzger, 2000; Dorr et al., 2001; Frazier, Moser, & Stone, 2001; Holden & Naleway, 2001; Holden & Therrien, 2000; Kasper, McNulty, Otto, & Thomas, 1993; Landis & Whitney, 1997; McCarthy, 2000; Page, Blakely, & Ben-Eliyahu, 2001; Stanley & Paice, 1997; Witek-Janusek & Ratmeyer, 1991). Many of these studies have evaluated molecular-genomic factors underlying health, disease, and injury recovery.

Nursing science, and health science research more broadly, is strengthened by nurses' unique ability to gain patient trust and subsequent insight into their lives, perceptions, and care needs. Thus, the inclusion of the nursing perspective enhances the design of pre-clinical studies by promoting selection of more clinically relevant variables likely to be key contributors to patient wellbeing and quality of life. As multi- and trans-disciplinary teams are becoming increasingly common, nurses should embrace opportunities to conduct and participate in animal research. In other words, the climate is right for nurse scientists to further establish themselves as leaders and key contributors to pre-clinical research. Funding agencies within the National Institutes of Health, including the National Institute of Nursing Research (NINR), in addition to other professional nursing organizations encourage and support pre-clinical studies. Among the studies funded are many collaborative research projects with nurses as PI's or dual-discipline co-investigators (co-Is). Moreover, many schools of nursing are becoming home to nurse scientists and other researchers using pre-clinical models in their work, and several schools have in-house pre-clinical research space for housing test animals and completing study activities.

Overall, nurses continue to make important contributions to animal research by applying pre-clinical methodologies, reviewing journal articles, being members of ethics review boards, and participating in study sections for granting agencies. Nurses in clinical practice assist with the efforts to translate findings from animal research to the bedside. As the prospects of using *pharmacogenomics* knowledge to inform precision medicine become increasingly possible, the applications of pre-clinical research will become even more quintessential. Recently, the research community has shown strong interest in how *animal models* can be applied to advance nursing science, and ultimately be translated to nursing practice (Holtzclaw & Hanneman, 2002; Kasper, 2013; Schumacher, 2010; Tkacs & Thompson, 2006b). The research community at large touts a seasoned history of using *animal models* to make substantial contributions to the understanding and treatment of a plethora of human health conditions. While the intersection of nursing science with preclinical *animal models* is relatively new, it represents a promising, robust, and growing area of research.

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References

Anderson G, Alt-White AC, Schaa KL, Boyd AM, Kasper CE. Genomics for Nursing Education and Practice: Measuring Competency. Worldviews on Evidence-Based Nursing / Sigma Theta Tau International, Honor Society of Nursing. 2015; 12(3):165–75. doi:10.1111/wvn.12096.

Bennetts P, Shen Q, Thimmesch AR, Diaz FJ, Clancy RL, Pierce JD. Effects of ubiquinol with fluid resuscitation following haemorrhagic shock on rat lungs, diaphragm, heart and kidneys. Experimental Physiology. 2014; 99(7):1007–15. doi:10.1113/expphysiol.2014.078600. [PubMed: 24860150]

Bhattacharya D, Marfo CA, Li D, Lane M, Khokha MK. CRISPR/Cas9: An inexpensive, efficient loss of function tool to screen human disease genes in Xenopus. Developmental Biology. 2015; 408(2): 196–204. doi:10.1016/j.ydbio.2015.11.003. [PubMed: 26546975]

Blaumanis OR, Rennels ML, Grady PA. Focal cerebral edema impedes convective fluid/tracer movement through paravascular pathways in cat brain. Advances in Neurology. 1990; 52:385–9. [PubMed: 2396535]

Blix A. Personalized medicine, genomics, and pharmacogenomics: a primer for nurses. Clinical Journal of Oncology Nursing. 2014; 18(4):437–41. doi:10.1188/14.CJON.437-441. [PubMed: 25095297]

Bomont P, Cavalier L, Blondeau F, Ben Hamida C, Belal S, Tazir M, Koenig M. The gene encoding gigaxonin, a new member of the cytoskeletal BTB/kelch repeat family, is mutated in giant axonal neuropathy. Nature Genetics. 2000; 26(3):370–4. doi:10.1038/81701. [PubMed: 11062483]

Bond EF, Heitkemper MM, Bailey SL. Estrogen suppresses gastric motility response to thyrotropin-releasing hormone and stress in awake rats. Research in Nursing & Health. 1998; 21(3):221–8. [PubMed: 9609507]

Briones TL, Therrien B, Metzger B. Effects of environment on enhancing functional plasticity following cerebral ischemia. Biological Research for Nursing. 2000; 1(4):299–309. [PubMed: 11232208]

Callaway E. Gene-editing research in human embryos gains momentum. Nature. 2016; 532(7599): 289–90. doi:10.1038/532289a. [PubMed: 27111607]

Citton V, Toldo I, Calderone M, Sartori S, Manara R. Early cortical cytotoxic edema in meningococcal meningitis. Pediatric Neurology. 2009; 41(2):146–50. doi:10.1016/j.pediatrneurol.2009.02.021. [PubMed: 19589467]

Dorr RT, Liddil JD, Sami SM, Remers W, Hersh EM, Alberts DS. Preclinical antitumor activity of the azonafide series of anthracene-based DNA intercalators. Anti-Cancer Drugs. 2001; 12(3):213–20. [PubMed: 11290869]

Dorsey SG, Leitch CC, Renn CL, Lessans S, Smith BA, Wang XM, Dionne RA. Genome-wide screen identifies drug-induced regulation of the gene giant axonal neuropathy (Gan) in a mouse model of antiretroviral-induced painful peripheral neuropathy. Biological Research for Nursing. 2009; 11(1):7–16. doi:10.1177/1099800409332726. [PubMed: 19398414]

Dorsey SG, Renn CL, Carim-Todd L, Barrick CA, Bambrick L, Krueger BK, Tessarollo L. In vivo restoration of physiological levels of truncated TrkB.T1 receptor rescues neuronal cell death in a trisomic mouse model. Neuron. 2006; 51(1):21–8. doi:10.1016/j.neuron.2006.06.009. [PubMed: 16815329]

Foundation for Biomedical Research. Thanks to animal research, they'll be able to protest 20.8 years longer. 2006. Retrieved from https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101438472-img

Frazier SK, Moser DK, Stone KS. Heart rate variability and hemodynamic alterations in canines with normal cardiac function during exposure to pressure support, continuous positive airway pressure,

and a combination of pressure support and continuous positive airway pressure. Biological Research for Nursing. 2001; 2(3):167–74. [PubMed: 11547538]

Funk JL, Frye JB, Davis-Gorman G, Spera AL, Bernas MJ, Witte MH, Ritter L. Curcuminoids limit neutrophil-mediated reperfusion injury in experimental stroke by targeting the endothelium. Microcirculation (New York, N.Y. : 1994). 2013; 20(6):544–54. doi:10.1111/micc.12054.

Funk JL, Migliati E, Chen G, Wei H, Wilson J, Downey KJ, Ritter LS. Parathyroid hormone-related protein induction in focal stroke: a neuroprotective vascular peptide. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2003; 284(4):R1021–30. doi: 10.1152/ajpregu.00436.2002.

Goodyear-Bruch CA, Jegathesan J, Clancy RL, Pierce JD. Apoptotic-related protein expression in the diaphragm and the effect of dopamine during inspiratory resistance loading. Biological Research for Nursing. 2008; 9(4):293–300. doi:10.1177/1099800408314573. [PubMed: 18398224]

Hampton T. Ethical and Societal Questions Loom Large as Gene Editing Moves Closer to the Clinic. JAMA. 2016; 315(6):546–8. doi:10.1001/jama.2015.19150. [PubMed: 26810772]

Holden JE, Naleway E. Microinjection of carbachol in the lateral hypothalamus produces opposing actions on nociception mediated by alpha(1)- and alpha(2)-adrenoceptors. Brain Research. 2001; 911(1):27–36. [PubMed: 11489441]

Holden JE, Therrien B. The effect of familiarity on distraction and single cue use after hippocampal damage. Biological Research for Nursing. 2000; 1(3):165–78. [PubMed: 11232212]

Holtzclaw BJ, Hanneman SK. Use of non-human biobehavioral models in critical care nursing research. Critical Care Nursing Quarterly. 2002; 24:30–40. [PubMed: 11833627]

Kasper CE. Animal models of exercise and obesity. Annu Rev Nurs Res. 2013; 31:1–17. doi: 10.1891/0739-6686.31.1. [PubMed: 24894135]

Kasper CE, McNulty AL, Otto AJ, Thomas DP. Alterations in skeletal muscle related to impaired physical mobility: an empirical model. Research in Nursing & Health. 1993; 16(4):265–73. [PubMed: 8378556]

Kuhlenbäumer G, Young P, Oberwittler C, Hünermund G, Schirmacher A, Domschke K, Stögbauer F. Giant axonal neuropathy (GAN): case report and two novel mutations in the gigaxonin gene. Neurology. 2002; 58(8):1273–6. [PubMed: 11971098]

Lan S-Y, Lin J-J, Hsia S-H, Wang H-S, Chiu C-H, Lin K-L, CHEESE Study Group. Analysis of Fulminant Cerebral Edema in Acute Pediatric Encephalitis. Pediatrics and Neonatology. 2016 doi: 10.1016/j.pedneo.2015.11.002.

Landis CA, Whitney JD. Effects of 72 hours sleep deprivation on wound healing in the rat. Research in Nursing & Health. 1997; 20(3):259–67. [PubMed: 9179179]

Leach V, Tonkin E, Lancastle D, Kirk M. A strategy for implementing genomics into nursing practice informed by three behaviour change theories. International Journal of Nursing Practice. 2016; 22(3):307–15. doi:10.1111/ijn.12431. [PubMed: 27241441]

Ledford H. CRISPR: gene editing is just the beginning. Nature. 2016; 531(7593):156–9. doi: 10.1038/531156a. [PubMed: 26961639]

LePage DF, Conlon RA. Animal models for disease: knockout, knock-in, and conditional mutant mice. Methods in Molecular Medicine. 2006; 129:41–67. doi:10.1385/1-59745-213-0:41. [PubMed: 17085804]

Li HS, Hultcrantz M. Age-related degeneration of the organ of Corti in two genotypes of mice. ORL; Journal for Oto-Rhino-Laryngology and Its Related Specialties. 1994; 56(2):61–67. doi: 10.1159/000276611. [PubMed: 8177586]

Lira FS, Rosa JC, Pimentel GD, Santos RV, Carnier J, Sanches PL, Dâmaso AR. Long-term interdisciplinary therapy reduces endotoxin level and insulin resistance in obese adolescents. Nutrition Journal. 2012; 11:74. doi:10.1186/1475-2891-11-74. [PubMed: 22989045]

Long C, Amoasii L, Mireault AA, McAnally JR, Li H, Sanchez-Ortiz E, Olson EN. Postnatal genome editing partially restores dystrophin expression in a mouse model of muscular dystrophy. Science (New York, N.Y.). 2016; 351(6271):400–3. doi:10.1126/science.aad5725.

Low BE, Wiles MV. A Humanized Mouse Model to Study Human Albumin and Albumin Conjugates Pharmacokinetics. Methods in Molecular Biology (Clifton, N.J.). 2016; 1438:115–22. doi: 10.1007/978-1-4939-3661-8_7.

Mashimo T, Serikawa T. Rat resources in biomedical research. Current Pharmaceutical Biotechnology. 2009; 10(2):214–20. [PubMed: 19199954]

Matthews KA, Kaufman TC, Gelbart WM. Research resources for Drosophila: the expanding universe. Nature Reviews Genetics. 2005; 6(3):179–193. doi:10.1038/nrg1554.

McCarthy DO. Tumor necrosis factor alpha and interleukin-6 have differential effects on food intake and gastric emptying in fasted rats. Research in Nursing & Health. 2000; 23(3):222–8. [PubMed: 10871537]

McClearn GE, Rodgers DA. Genetic factors in alcohol preference of laboratory mice. Journal of Comparative and Physiological Psychology. 1961 doi:10.1037/h0042530.

Melo JA, Shendure J, Pociask K, Silver LM. Identification of sex-specific quantitative trait loci controlling alcohol preference in C57BL/ 6 mice. Nature Genetics. 1996; 13:147–153. doi: 10.1038/ng0696-147. [PubMed: 8640219]

Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. JRSM. 2011; 104(12):510–520. doi:10.1258/jrsm.2011.110180.

National Research Council. Guide for the Care and Use of Laboratory Animals. 8th ed.. C. for the U. of the G. for the C. and U. of L. Animals & N. R. Council. , editor. The National Acadamies Press; Washington, D.C.: 2010.

Nelson CE, Hakim CH, Ousterout DG, Thakore PI, Moreb EA, Castellanos Rivera RM, Gersbach CA. In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy. Science (New York, N.Y.). 2016; 351(6271):403–7. doi:10.1126/science.aad5143.

Page GG. The importance of animal research to nursing science. Nursing Outlook. 2004; 52(2):102–7. discussion 108–10. doi:10.1016/j.outlook.2003.10.011. [PubMed: 15073591]

Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain. 2001; 90(1-2):191–9. [PubMed: 11166986]

Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA. Evidence for a “Paravascular” fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Brain Research. 1985; 326(1):47–63. doi:10.1016/0006-8993(85)91383-6. [PubMed: 3971148]

Ritter L. Ischemia-reperfusion injury after stroke: from mechanisms to a nursing process. Nursing Science Quarterly. 2008; 21(1):41–2. [PubMed: 18246645]

Ritter L, Davidson L, Henry M, Davis-Gorman G, Morrison H, Frye JB, Funk JL. Exaggerated neutrophil-mediated reperfusion injury after ischemic stroke in a rodent model of type 2 diabetes. Microcirculation (New York, N.Y. : 1994). 2011; 18(7):552–61. doi:10.1111/j. 1549-8719.2011.00115.x.

Ritter L, Funk J, Schenkel L, Tipton A, Downey K, Wilson J, McDonagh P. Inflammatory and hemodynamic changes in the cerebral microcirculation of aged rats after global cerebral ischemia and reperfusion. Microcirculation (New York, N.Y. : 1994). 2008; 15(4):297–310. doi: 10.1080/10739680701713840.

Rodgers B, Anderko L. The importance of animal research to nursing science. Nursing Outlook. 2004; 52(4):164. author reply 164–5. [PubMed: 15328501]

Rowsey PJ. Using Animals in Nursing Research: Bridging Gaps Between Bench, Bedside, and Practice. Western Journal of Nursing Research. 2015; 37(12):1515–1516. doi: 10.1177/0193945915578815. [PubMed: 25845804]

Rowsey PJ, Borer KT, Kluger MJ. Role of prostaglandins in exercise-induced core temperature elevation in female Sprague-Dawley rats. The American Journal of Physiology. 1993; 265(5 Pt 2):R1121–5. [PubMed: 8238613]

Rowsey PJ, Gordon CJ. Tolerance to the hypothermic and hyperthermic effects of chlorpyrifos1This paper has been reviewed by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade n. Toxicology. 1997; 121(3):215–221. doi:10.1016/S0300-483X(97)00068-1.

Rowsey PJ, Gordon CJ. A peripheral mechanism of fever: differential sensitivity to the antipyretic action of methyl scopolamine. Autonomic Neuroscience. 2000; 85(1-3):148–155. doi:10.1016/ S1566-0702(00)00234-4. [PubMed: 11189022]

Rowsey PJJ, Metzger BLL, Carlson J, Gordon CJJ. Long-Term Exercise Training Selectively Alters Serum Cytokines Involved in Fever. Biological Research For Nursing. 2009; 10(4):374–380. doi:10.1177/1099800408329409. [PubMed: 19190031]

Rowsey PJ, Metzger BL, Carlson J, Gordon CJ. Effects of exercise conditioning on thermoregulatory responses to repeated administration of chlorpyrifos. Environmental Research. 2003; 92(1):27–34. doi:10.1016/S0013-9351(02)00096-8. [PubMed: 12706752]

Rowsey PJ, Metzger BL, Carlson J, Gordon CJ. Effects of chronic exercise conditioning on thermal responses to lipopolysaccharide and turpentine abscess in female rats. Archives of Toxicology. 2006; 80(2):81–87. doi:10.1007/s00204-005-0036-2. [PubMed: 16254718]

Ruehl ML, Orozco JA, Stoker MB, McDonagh PF, Coull BM, Ritter LS. Protective effects of inhibiting both blood and vascular selectins after stroke and reperfusion. Neurological Research. 2002; 24(3):226–32. doi:10.1179/016164102101199738. [PubMed: 11958413]

Sadler GR, Lantz JM, Fullerton JT, Dault Y. Nurses' unique roles in randomized clinical trials. Journal of Professional Nursing. 1999; 15(2):106–115. doi:10.1016/S8755-7223(99)80081-7. [PubMed: 10194895]

Schumacher AM. Integrating animal model research into perianesthesia nursing practice. Journal of Perianesthesia Nursing. 2010; 25:212–213. doi:10.1016/j.jopan.2010.06.001. [PubMed: 20656256]

Schutte DL. Integrating Molecular Genetics Analyses Into Clinical Research. Biological Research For Nursing. 2006; 8(1):67–77. doi:10.1177/1099800406289909. [PubMed: 16766630]

Seibert DC. Genomics and nurse practitioner practice. The Nurse Practitioner. 2014; 39(10):18–28. quiz 28–9. doi:10.1097/01.NPR.0000453641.13662.03.

Smith SA. Zebrafish resources on the internet. ILAR Journal / National Research Council, Institute of Laboratory Animal Resources. 2012; 53(2):208–14. doi:10.1093/ilar.53.2.208.

Stanley KL, Paice JA. Animal models in pain research. Seminars in Oncology Nursing. 1997; 13(1):3–9. [PubMed: 9048430]

Statler KD, Alexander H, Vagni V, Holubkov R, Dixon CE, Clark R, Kochanek PM. Isoflurane exerts neuroprotective actions at or near the time of severe traumatic brain injury. Brain Research. 2006; 1076(1):216–24. doi:10.1016/j.brainres.2005.12.106. [PubMed: 16473332]

Statler KD, Kochanek PM, Dixon CE, Alexander HL, Warner DS, Clark RS, Safar PJ. Isoflurane improves long-term neurologic outcome versus fentanyl after traumatic brain injury in rats. Journal of Neurotrauma. 2000; 17(12):1179–89. [PubMed: 11186231]

The Jackson Laboratory. Strain Name: C57BL/6J. 2013. Retrieved from http://jaxmice.jax.org/strain/010561.html

Tkacs NC, Li J. Immune stimulation induces Fos expression in brainstem amygdala afferents. Brain Research Bulletin. 1999; 48:223–231. doi:10.1016/S0361-9230(98)00167-1. [PubMed: 10230714]

Tkacs NC, Li J, Strack AM. Central amygdala Fos expression during hypotensive or febrile, nonhypotensive endotoxemia in conscious rats. Journal of Comparative Neurology. 1997; 379:592–602. doi:10.1002/(SICI)1096-9861(19970324)379:4<592::AID-CNE9>3.0.CO;2-Y. [PubMed: 9067845]

Tkacs N, Dunn-Meynell A, Levin B. Presumed apoptosis and reduced arcuate nucleus neuropeptide Y and pro- opiomelanocortin mRNA in non-coma hypoglycemia. Diabetes. 2000; 49:820–826. doi:10.2337/diabetes.49.5.820. [PubMed: 10905492]

Tkacs N, Thompson H. From bedside to bench and back again: research issues in animal models of human disease. Biological Research for Nursing. 2006; 8(1):78–88. doi:10.1177/1099800406289717. [PubMed: 16766631]

Turner C. Antisense therapy: therapeutic magic bullet or theoretical dream? Clinical Oncology (Royal College of Radiologists (Great Britain)). 1997; 9(1):54–8. [PubMed: 9039815]

Umberger R, Holston EC, Hutson SP, Pierce M. Nursing genomics: practice implications every nurse should know. The Nursing Clinics of North America. 2013; 48(4):499–522. doi:10.1016/j.cnur.2013.08.006. [PubMed: 24295185]

Unterberg AW, Stover J, Kress B, Kiening KL. Edema and brain trauma. Neuroscience. 2004; 129(4):1021–9. doi:10.1016/j.neuroscience.2004.06.046. [PubMed: 15561417]

Wagner JL, Zhou FC, Goodlett CR. Effects of one- and three-day binge alcohol exposure in neonatal C57BL/6 mice on spatial learning and memory in adolescence and adulthood. Alcohol. 2014; 48:99–111. doi:10.1016/j.alcohol.2013.12.001. [PubMed: 24507877]

Watson AJ, Henson K, Dorsey SG, Frank MG. The truncated TrkB receptor influences mammalian sleep. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology. 2015; 308(3):R199–R207. doi:10.1152/ajpregu.00422.2014.

Weizmann Institute of Sciences. Zechi-Ceide Syndrome. 2015. Retrieved from http://www.malacards.org/card/zechi_ceide_syndrome

Williams JK, Cashion AK, Shekar S, Ginsburg GS. Genomics, clinical research, and learning health care systems: Strategies to improve patient care. Nursing Outlook. 2016; 64(3):225–8. doi: 10.1016/j.outlook.2015.12.006. [PubMed: 26821732]

Witek-Janusek L. Maternal ethanol ingestion: effect on maternal and neonatal glucose balance. The American Journal of Physiology. 1986; 251(2 Pt 1):E178–84. [PubMed: 3526919]

Witek-Janusek L. Pituitary-adrenal response to bacterial endotoxin in developing rats. The American Journal of Physiology. 1988; 255(4 Pt 1):E525–30. [PubMed: 2845803]

Witek-Janusek L. Commentary on the importance of animal research to nursing science. Nursing Outlook. 2004; 52(2):108–110. doi:10.1016/j.outlook.2003.10.012.

Witek-Janusek L, Ratmeyer JK. Sepsis in the young rat: maternal milk protects during cecal ligation and puncture sepsis but not during endotoxemia. Circulatory Shock. 1991; 33(4):200–6. [PubMed: 2065440]

Yelich MR, Witek-Janusek L. Glucose, lactate, insulin, and somatostatin responses to endotoxin in developing rats. Shock (Augusta, Ga.). 1994; 2(6):438–44.

Zheng H, Chen C, Zhang J, Hu Z. Mechanism and Therapy of Brain Edema after Intracerebral Hemorrhage. Cerebrovascular Diseases (Basel, Switzerland). 2016; 42(3-4):155–69. doi: 10.1159/000445170.

Table 1

Glossary

Term	Definition
Allele	A specific version of a given gene. For some genes, there may be one or more allele(s) associated with a change in phenotype (e.g. disease risk) compared to the normal version of the gene (i.e. wildtype allele). For other genes there may be variation as evidenced by two or more alleles in the population, but there are no known resulting differences in phenotype. Note: Each individual has two alleles for each gene (because humans have 23 pairs of chromosomes, with one member of each pair inherited from their mother and the other from their father). In some cases, one copy of a particular allele results in the associated phenotype, while in other cases two copies of the allele are needed to produce the phenotype
Animal model	A non-human animal used to study a clinical problem in biomedical research that shares similar physiological and/or functional characteristics with humans of a particular clinical population. In some instances, the species used is already afflicted by a disease common to humans, and other times, a clinical condition is mimicked in animals as part of the experimental procedures. Animal models are used when a question could not be practically, ethically, or safety studied in humans, and they may lay the groundwork for future clinical inquiry and changes in practice.
Autosomal dominant	A pattern of trait inheritance where the given phenotype results when the individual possesses at least one copy of the associated allele, which exists on one of the autosomes (i.e. a numbered chromosome, not the X or Y chromosome). This is in contrast to autosomal recessive conditions, which require 2 copies of the associated allele for the individual to display the phenotype.
Chromosome	A condensed package of DNA found within the nucleus of a cell. Humans have 46 chromosomes in 23 pairs (with one member of each pair coming from each parent). Other types of animals have different numbers of chromosomes. There are two major types of chromosomes: autosomes (numbered chromosomes; 1-22 in humans) and sex chromosomes (X and Y).
Complementary deoxyribonucleic acid (cDNA)	A laboratory-produced doubled stranded DNA molecule. In the context of animal models, cDNA is often used to modify the genomes of test animals, as is the case when generating a knockin animal.
Deoxyribonucleic Acid (DNA)	The scientific name for the molecule that contains the genetic information coding for all the proteins comprising a given organism. DNA molecules are double stranded molecules wound together in the form of a double helix.
Conditional (i.e. inducible) mutation	When a given genotype for a particular gene only results in the phenotype of interest under certain environmental conditions. For example, individuals with sickle cell disease only exhibit symptoms of the condition under restrictive environments (e.g. cold; low oxygen; emotional stress).
Gene	A stretch of DNA encoding some trait or protein of interest. Genes are passed on from parents to offspring in the sperm and egg, which contain chromosomes; each chromosome has many genes along it.
Gene Expression	The process of producing a protein using the code contained in the DNA. Each set of 3 DNA bases corresponds to a particular amino acid; consecutive amino acids are strung together as a polypeptide, also known as a protein.
Genome	The full set of genetic information for a given organism. Each cell in the organism possesses the full genome within it, mostly in the nucleus (which contains chromosomes), and to a lesser extent in extra-chromosomal mitochondrial DNA.
Genetics	Using scientific techniques to study a particular gene or set of genes.
Genomics	Using scientific techniques to study the entire genome of an organism as opposed to a single gene or small set of related genes (i.e. genetics).
Genotype	The collection of genes possessed by an individual organism that directs protein production and ultimately affects the individual's observable traits (i.e. phenotype). Note: depending on the context, sometimes the term is used to describe the composition of alleles that an individual possesses for a particular gene in the genome.
Heterozygous	An individual who has two different alleles for a particular gene, having received different versions from their mother and father.
Homozygous	An individual who has two of the same alleles for a particular gene, having received identical versions from their mother and father.
In Vitro	A process that happens outside of a living organism. The term literally translates to “in glass” because in vitro experiments often happen in in a Petri dish or test tube.
In Vivo	A process that happens inside of a living organism. The term literally translates to “in life” because in vivo processes occur within a human organism or other animal.

Term	Definition
Knockin	Use of molecular genomic techniques to add genetic information to an organism. This is often done as part of the effort to humanize a test animal to better mimic a clinical population.
Knockout	Use of molecular genomic techniques to remove genetic information from an organism or make the copy non-functional.
Locus/loci	The physical location of a particular gene or stretch of genetic material along a chromosome. When more than one locus is being referred to, they are called “loci.”
Mouse model	Use of a mouse to study a condition that affects humans; a specific type of animal model.
Nucleotide	The most fundamental building block of genetic material (e.g. DNA). Nucleotides have 3 components, a sugar (ribose or deoxyribose), a phosphate group, and a nitrogen-containing base (adenine, guanine, thymine, cytosine, and uracil).
Pharmacogenomics	The intersection of genomic information and pharmacology. Applications include identifying the correct therapeutic regimen based on a patient's genotype and correlating drug response with genotype.
Phenotype	The traits that can be observed or measured in an individual (e.g. hair color; disease presence/absence; height). The phenotype is produced by the genotype when the gene(s) involved are expressed into protein(s); there may also be an impact of environmental factors (e.g. diet; exercise; sun-exposure) on phenotype.
Strain	A population of test animals that are genetically uniform as a result of inbreeding or genetic engineering.
Substrain	A subpopulation of a strain of test animals, uniquely characterized because they have some distinguishing feature from the parent strain, usually as the result of genetic changes that accumulate over several generations of breeding.
Transgenic	A transgenic animal is one who has had DNA from another source inserted into its genome using laboratory techniques.

Table 2

Resources

Resource Name	Sponsor/Source	Description	URL
Mouse Genome Informatics	The Jackson Laboratory with data contributed form several well-known research groups	International database providing a wealth of data (e.g. genetic, genomic, biological, phenotypic) about laboratory mice used in biomedical research. Selected resources include a glossary, a wealth of readings, data, and other downloadable resources.	www.informatics.jax.org
International Mouse Strain Resource	IMSR funded by National Institutes of Health (NTH)	A database that assists researchers with acquiring information about mice of various strains including sources of these mice for use in research.	www.findmice.org
UCSC Mouse Genome Browser	Genome Bioinformatics Group of UC Santa Cruz	Complete mouse genome information for the most commonly used strain of mice in biomedical research (C57BL/6). Note: genomes of other species of animal are also available through the genome browser, though the link provided is for the mouse browser specifically.	http://genome.ucsc.edu/cgi-bin/hgGateway?org=mouse
Mammalian Gene Collection	NIH	Validated sequence information in a convenient, searchable form. Note: also includes genomic sequence	http://genecollections.nci.nih.gov/MGC/

Resource Name	Sponsor/Source	Description	URL
		information for human, rat, and cow.	
Mouse Genome Assembly Data	Genome Reference Consortium	Searchable website that provide global mouse assembly statistics and data for mice with periodic reviews and patch releases of data. Note: also contains genomic reference information for human, zebrafish, and chicken.	https://www.ncbi.nlm.nih.gov/projects/genome/assembly/grc/mouse/data/
Mouse Genomes Project	Wellcome Trust (WT); Sanger Institute	Provides data and complete sequence information for many inbred strains of mice used in biomedical research. There is also a mouse genome variant querying site. Sequencing reads, variants, and assembled genome sequences are published on this site. With permission, researchers can download data and use it for analysis and publication.	http://www.sanger.ac.uk/resources/mouse/genomes/
Knockout Mouse Phenotyping Project	NIH in collaboration between the Jackson Laboratory, Baylor College of Medicine, the University of California Davis, and others	Provides a functional catalog of a mammalian genome through systematic generation and phenotyping of 20,000 knockout strains. The website provides searchable genotype and phenotype information.	http://www.mousephenotype.org/
Current Lab Codes	Institute for Laboratory Animal Research (ILAR)	International registry of laboratory codes	http://dels.nas.edu/global/ilar/Lab-Codes

Resource Name	Sponsor/Source	Description	URL
		indicating the institute, laboratory, or investigator where a particular strain of test animal was produced and/or is maintained. In addition to strains, substrains, congenic strains, other distinguishable groups of strains, DNA loci, specific mutations, and other chromosomal aberrations may have a laboratory code.	
Knockout Mouse Project (KOMP) Repository	UC Davis	The ultimate goal is a comprehensive resource that is publically available and comprises mouse embryonic stem cells that have knocked out genes of each and every gene in the mouse genome. The repository is updated regularly, following acquisition of new vectors, cell lines, and live mice.	https://www.komp.org/
European Nucleotide Archive	European Molecular Biology Laboratory, Seventh Framework Programme of the European Commission, the British Biotechnology & Biological Sciences Research Council, and the WT	Provides a comprehensive guide to nucleotide sequencing information which covers sequence assembly information, raw data generated during sequencing, and also functional annotation.	http://www.ebi.ac.uk/ena
Mutant Mouse Resource Research Centers (MMRRC)	NIH	A national network of mouse	https://www.mmrrc.org/

Resource Name	Sponsor/Source	Description	URL
		breeding and distribution facilities dedicated to being a high-quality repository of mouse strains, including many that are not commercially available. Researchers can also donate to this resource as part of their obligation to share grant-funded resources (if applicable).	