**ILAR J**

Volume 58, Number 1, 2017

***Bridging the Gap between Reproducibility and Translation: Data Resources and Approaches***

**Zeiss and Johnson. Bridging the Gap between Reproducibility and Translation: Data Resources and Approaches, pp. 1-3**

Domain 3: Research

SUMMARY: Animals are important models of disease, but in some research areas these models fail to translate to the clinic. Translational barriers include the divergence of the transcriptomic response, mismatch of temporal response patterns, differences in both innate and adaptive immunity, and heterogeneity within humans in comparison to inbred mice.

Bioinformatics technologies such as genomics and transcriptomics are used to demonstrate common disease mechanisms or pathways across species. In this ILAR issue, use of genomics resources are described for zebrafish, mice, rats, and nonhuman primates, as well as the use of transcriptomics in toxicologic pathology. In addition to expanding bioinformatics data, there has also been an explosion of text-based data that is not easily integrated or accessed.

The trade-off between internal and external validity is one potential reason why results from animal models do not generalize to humans. Minimizing bias is central to internal validity, but it often provides results that fail to generalize to other situations. Authors in this issue explore factors that contribute to the reproducibility-translatability gap in sepsis and neurodegenerative disease models, including relationships between model choice, intended goal of the intervention, pharmacologic criteria, and integration of biomarker data with outcome measures that are clinically relevant to humans.

QUESTIONS

1. Two specific areas of disease research that struggle with translation of animal models are \_\_\_\_\_\_\_\_ and \_\_\_\_\_\_\_\_\_.

2. Minimizing bias increases \_\_\_\_\_\_ validity, but often decreases \_\_\_\_\_\_ validity.

a. Internal, external

b. External, internal

c. Internal, discriminant

d. Predictive, external

ANSWERS

1. Neurodegenerative disorders, sepsis

2. a

**Bradford et al. Zebrafish Models of Human Disease: Gaining Insight into Human Disease at ZFIN, pp. 4-16**

Secondary Species: Zebrafish (*Danio rerio*)

SUMMARY: Zebrafish (*Danio rerio*) have been used in research since the 1960’s, but did not really become a very popular model for any human disease until the 1980’s when George Streisinger began doing genetic analysis and mutations with them.  They are now primarily used to study genetics, developmental biology, and gene function due in part to their high fecundity, optical clarity of embryos, extrauterine development, quick maturation reaching larval stage by 72 hours post fertilization, and ease of genetic manipulation.  Their genome has a high degree of genetic similarity with humans and provides a venue to understand gene function.  Zebrafish Model Organism Database (ZFIN) is a database of the different zebrafish diseases and the human diseases that correlate with them.  In the ZFIN database it is important to use standard nomenclature.  The formula is Background + Genotype + STR (Sequence Targeting Reagent).  Because environmental conditions can have a major effect on the development of human diseases ZFIN includes ZECO (Zebrafish Environmental Conditions Ontology) so that conditions can be repeated.  ZNI categorizes their models in a few ways.  First there are based on alteration of disease-associated genes (what disease occurs when a normal human ortholog is disrupted in the Zebrafish?).  Second, what happens when a normal gene is expressed at in irregular time or in an irregular tissue?  Third, what happens when fish are exposed to disease causing conditions?  The last part of this paper goes over the steps to discovering the human diseases that have already been recapitulated in Zebrafish.

QUESTIONS

1. How many chromosomes does *Danio rerio* have (haploid)?

a. 21

b. 23

c. 25

d. 28

2. Used with *Danio rerio*, what is the primary use of N-ethyl-N-nitrosourea (ENU)?

a. Analgesia

b. Mutagenesis

c. Anesthesia

d. Antimicrobial

3. For *Danio rerio*, at what time point after fertilization does gastrulation start?

a. 5.5 hours

b. 10 hours

c. 15 hours

d. 24 hours

ANSWERS

1. c

2. b

3. a

**Eppig. Mouse Genome Informatics (MGI) Resource: Genetic, Genomic, and Biological Knowledgebase for the Laboratory Mouse, pp. 17-41**

Primary Species: Mouse (*Mus musculus*)

SUMMARY: As the mouse has become the most important genetic animal model, this review of the Mouse Genome Informatics (MGI) resource touches on the key advantages of mice as an experimental tool and lists other resources that have been key in genetic studies.  MGI is a member of the Alliance for Genome Resources, which also includes databases related to other model organism.  The mission of the MGI resource is to provide integrated genetic, genomic, and biological data about the laboratory mouse to facilitate the study of human health and disease.  The MGI has maintained a history of crucial discoveries using transgenic and knock-out mouse models, technological advancements (such as the internet and DNA sequencing), genetic engineering technology (such as TALENs and CRISPR/Cas9) and other tools (such as the Collaborative Cross) that have encouraged and informed the use of the mouse as a genetic tool. Eppig discusses the importance of scientific communication standards and use of proper and standardized vocabulary and nomenclature when employing an informatics database in order to do proper searches for desired phenotypes.  The author provides links to nomenclature guidelines for 10 species, from single-celled Saccharomyces up to humans, and including zebrafish, *Xenopus*, chicken, and rodents.  The author discusses how various biotechnological tools (such as mutagenesis with ENU, reverse mutagenesis and the International Mouse Knockout Consortium, conditional mutagenesis, genome editing strategies) have impacted the use of the mouse as a genetic model. Gene modification is only as useful as our ability to understand the relationship with anatomic, disease, developmental, and behavioral phenotypes.  Thus, efforts to establish globally standardized phenotyping procedures were initially studied in Europe using four inbred mouse strains (C57BL/6J, C3HeB/FeJ, BALB/cByJ, and 129S2/SvPas). Phenotyping standards are being spearheaded by the International Mouse Phenotyping Consortium and efforts have been expanded across multiple laboratories to phenotype over 650 mutant mouse lines. The MGI database can be searched at<http://www.informatics.jax.org/>.  It has resources on specific genes and mutations, gene phenotyping and phenotypic analysis results for various mouse strains, gene expression data, mouse models of human diseases, gene ontology and mouse ortholog tools, and even more tools organized within tabbed menus and accessed with query forms. Eppig’s review is a comprehensive guide to the MGI database and its capabilities will be increased as more information becomes available.

QUESTIONS

1.   Although the mouse had been domesticated for some time, the mouse ascended to a “tractable, exceptional experimental system” after the following discovery

a.  1902—Cuenot’s demonstration that Mendelian genetic principles apply to mammals in coat color research

b.  1909—Work by Nicolle on the transmission of human typhus, using studies of murine typhus

c.  1915—Haldane’s report is published, leading to genetic mapping in the mouse

d.  1933—Bittner’s work on the transmission of mammary tumors in mice

e.   1936—Doisy’s isolation of the antihemorrhagic factor Vitamin K

2.  True/False.  In just over 10 years, between 1985 and 1996, the advent of DNA technology with the ability to detect genetic polymorphisms precipitated the discovery of additional known mouse genetic markers on the linkage map and increased known markers by 10-fold.

3.  The precursor of the Mouse Genome Informatics database was known as the Mouse Gene Directory and Linkage Map.

4.   The goal of the European Eumorphia project (2006, 2008) was a collaborative effort to establish globally standardized phenotyping procedures.  Which strain was not one of the original four inbred strains from which baseline phenotypes were acquired?

a.  C57BL/6J

b.  C3HeB/FeJ

c.  BALB/cByJ

d.  129S2/SvPas

e.  NOD/LtJ

ANSWERS

1.  a. 1902—Cuenot’s work

2. True.  By 1996, the number of mapped polymorphisms was over 7,000

3.  False.  The precursor of the MGI was software entitled “Encyclopedia of the Mouse Genome”

4.  e. NOD/LtJ (this is an original Collaborative Cross founder strain)

**Shimoyama et al. Rat Genome and Model Resources, pp. 42-58**

**Primary Species:** Rat (*Rattus norvegicus*)

**Domain** 3: Research; K3 (animal models), K4 (genetics and nomenclature), K5 (genetic modifications/engineering), K10 (information resources)

**SUMMARY**: Rat Genome Database (RGD) is the premier site for genomic and phenotype data; it also is the source of official nomenclature for rat genes, strains and QTLs. There are 738 inbred strains, 60 outbreds, 91 consomic, 1200 congenic, 131 RI, 13 segregating inbred, 706 mutants and 247 transgenic strains. Some of the interactive tools include: the InterViewer, which visualizes protein-protein interactions via physical associations, dephosphorylation reaction and colocalization; the PhenoMiner, a tool to identify models for study, which allows you to find phenotypic data from multiple strains and download data for measurements like heart and many others; the Variant Visualizer, which allows you to predict effects of changing a gene in various disease tracks. Finally, OLGA (Object List Generator & Analyzer) is a way of assembling data sets from rats, mice and humans based on functional similarities.

PhenoGen: is a way of applying systems genetics to do global analysis of molecular factors contributing to disease phenotypes (brain, liver and heart at present). It contains baseline data from the Hybrid Rat Diversity Panel (HRDP), a set of 96 genetically stable strains. This is used to link genetic variation to phenotype variation. The researcher can start with either a phenotype, and identify the QTL and genes associated with it; or start with a genotype and identify possible therapeutic targets or adverse consequences of current therapies. Specialized datasets from a RI strain (males only) have been included in complex ways. The plan is to add data from female rats, and to include RNA expression derived from RNA-Seq instead of microarrays.

Gene Editing Rat Resource Center (GERRC): is an NHLBI-funded source of genetically modified rats on different background strains. Requests for strain development undergoes scientific review focusing on the potential utility, relevance to NHLBI, and rationale for needing the new model in rats (especially if it already exists in the mouse). GERRC is an outgrowth of the originally-developed rat knockouts using zinc-finger nucleases; now it also uses TALEN, CRISPR/Cas9, and Sleeping Beauty to target 91 genes on 15 different background strains. Phenotype data are placed into PhenoMiner as they are published, and the strains are shared with other researchers.

Rat Resource and Research Center (RRRC): rederives and cryopreserves valuable rat lines, and distributes them to researchers who need them. Criteria for accepting a strain include estimates of its value and demand, availability from other sources, and difficulty of maintenance. 5-10 breeding pairs of a selected strain are used to establish a colony for rederivation and cryopreservation (sperm or embryos). For lines in high demand, live strains are maintained (15, currently). Sperm cryopreservation is used for single-gene mutations or transgenes on standard genetic backgrounds. The RRRC is one of the few labs in the world which successfully performs ICSI. It is also one of the only sources of rat ES cells; two germline competent ES cells have been characterized, both containing an EGFP reporter. They offer a variety of services relating to maintaining rat strains, including microinjection to generate knockouts or knockins. Every rat strain's information is available on their webpage including strain profile, genetic description and breeding/husbandry information. Their site links to the RGD. RRRC is affiliated with the University of Missouri (US) Comparative Medicine program, which trains lab animal residents and offers hands-on training for genotyping, cryopreservation, embryo manipulation, surgery, colony management and didactic courses.

National BioResource Project for the Rat in Japan (NBRP-Rat): collects, preserves and maintains 700 rat strains, does genotyping and phenotyping, and maintains a database. Cryopreserved embryos and sperm are available. Phenotype data on many mutants includes a range of behavioral, morphological and physiological phenotypes. Their genetic characterization of microsatellite markers enables pedigree charting; the chart shows the genetic distance (in %) between a selected strain and a list of 132 others.

Kyoto University Rat Mutant Archive (KURMA): repository of ENU-mutagenized rat DNA and frozen sperm. They can also use ZFN, TALEN or CRISPR/Cas9 for mutagenesis.

**QUESTIONS**

1. What is the premier source of information on rat genetics and phenotype data, as well as the official nomenclature site for rat genes, strains and QTLs?

a. Rat Genome Database

b. PhenoGen

c. Gene Editing Rat Resource Center

d. Rat Resource and Research Centre

e. National BioResource Project for the Rat

2. A researcher approaches you for help in locating assistance with restoring a mutant rat line for which she can obtain cryopreserved sperm. Which organization is most likely to be successful at this effort?

a. Rat Genome Database

b. PhenoGen

c. Gene Editing Rat Resource Center

d. Rat Resource and Research Centre

e. National BioResource Project for the Rat

3. Which information resource applies systems genetics to analyze molecular factors contributing to disease phenotypes?

a. Rat Genome Database

b. PhenoGen

c. Gene Editing Rat Resource Center

d. Rat Resource and Research Centre

e. National BioResource Project for the Rat

4. What does the chart below depict?

a. Phenotypic differences between rat strains

b. Popularity of various rat strains in genetics research

c. Genetic distance between rat strains

d. A tool for managing outbred rat breeding colonies

**ANSWERS**

1. a

2. d

3. b

4. c



**Harding. Genomic Tools for the Use of Nonhuman Primates in Translational Research, pp. 59-68**

Domain 3: Research

SUMMARY: Monkeys are important preclinical translational models for understanding the etiology of human diseases in many medical fields, including infectious disease, neurobiology, vision, metabolic disease, cardiovascular disease and reproduction. As more information is discovered about the genetic components of human diseases, it is reasonable to develop a better understanding of the genetic determinants that can influence the physiology of the nonhuman primate (NHP) models used in translational research. Characterization of NHP genetics may influence translational research by providing insights into whether there is sufficient homology (for specific genomic regions) to justify NHPs as a model for human disease; aiding in the development of models of specific diseases by finding and breeding natural variants within captive NHP populations; and finding aspects of NHP genetics that may influence the expression of a specific gene or pathway which is related to disease development in humans or related to the immune response to certain immunizations and pathogens. Knowing the genetic background of the captive monkeys used in experiments can help reduce experimental variation and enhance reproducibility.  This article summarizes the genomic and genetic resources available for five NHP species commonly used in research: rhesus macaques, cynomolgus macaques, baboons, African green monkeys, and marmosets. Whole genome sequences have been published for these five species, except for the baboon, and there are particularly advanced resources available for both rhesus and cynomolgus macaques.

QUESTIONS

1.  The transcriptome is defined as:

a.   The sequence of just the exomes of an animal

b.  The division of genetic subtypes based on geographic origin

c.  The complete set of transcripts (gene read outs) in a cell

d.  The de novo assembly of a genome

2.   Which of the following technologies has helped annotate the assembly of the rhesus genome by correcting mRNA coding sequences, identifying previously unknown mRNA isoforms, and characterizing noncoding RNAs that can influence gene expression?

a.  RNA-Seq

b.  DNA-Seq

c.   NextGen

d.  SNP array

3. Which of the following NHPs is the most widely used for translation research and for which there is the most info regarding genome structure and expression?

a.   Pigtail macaque

b.  Rhesus macaque

c.   Cynomolgus macaque

d.  Stump-tail macaque

ANSWERS

1.  c

2. a

3.   b

**Stiehl et al. The Utility of Gene Expression Profiling from Tissue Samples to Support Drug Safety Assessments, pp. 69-79**

Domain 3; TT3.10

SUMMARY: Transcriptomics is a part of toxicogenomics for preclinical assessment and it integrates genome-wide expression profiling with descriptive indicators of toxicology assessments to other genome-wide domains such as proteomics, metabolomics, and genetics.  Microarrays have been routine for toxicogenomics, but more recently Generation Sequencing technologies such as RNA sequencing have been used.  These two technologies have been coevolving with biostatistics workflows for expression analysis.  Most biostatistical models have developed to identify transcriptional alterations from in vitro systems.  However, toxicity-related expression changes in practice often do not reach the level of statistical significance.  Therefore, deconvolution, or the unmixing of transcriptomics signals at the level of tissue, cells and cellular processes is key to meaningful interpretation of the data.   Different algorithms calibrated against expression profiles derived from pure cell or tissue preps could predict the composition of tissue mixtures.  But silico deconvoluted tissue expression data-sets could conflict with downstream tissue expression data-sets.  Deconvolution analyses can overcome this using seed-genes with well-established function, to identify coexpressed genes.  Interpretation of tissue profiles in a holistic context allows conclusions based on evidence as compared to analysis of isolated gene expression data.  Some histological or tissue structures can be toxicity targets and if these structures are not abundant, gene expression changes may be difficult to recognize.

Toxicogenomics can be applied at different stages of drug development, including early target characterization, early in vitro target safety assessment, early in vivo testing in pharmacological models, early development and short-/mid-term nonclinical toxicology studies, and late development or long-term toxicology studies.  But while toxicogenomics is being developed and promised to provide relationships between molecular changes elicited by a compound and lesions subsequently in tissues, they have failed to deliver.  This is most likely due to the complexity of pathophysiological mechanisms within tissues.  Development of a large reference data set from clinical situations along with corresponding animal studies may help improve this failure.

QUESTIONS

1. What is transcriptomics and what is it used for?
2. What are the two technologies used in toxicogenomics?
3. What stages of drug development can toxicogenomics be applied to?

ANSWERS

1. Transcriptomics is a part of toxicogenomics for preclinical assessment and it integrates genome-wide expression profiling with descriptive indicators of toxicology assessments to other genome-wide domains such as proteomics, metabolomics, and genetics.
2. Microarrays have been routine for toxicogenomics, but more recently Generation Sequencing technologies such as RNA sequencing have been used.
3. Toxicogenomics can be applied at different stages of drug development, including early target characterization, early in vitro target safety assessment, early in vivo testing in pharmacological models, early development and short-/mid-term nonclinical toxicology studies, and late development or long-term toxicology studies.

**Rindflesch et al. Informatics Support for Basic Research in Biomedicine, pp. 80-89**

Domain 3: Research, K10 information resources

SUMMARY: Informatics is the science of processing data for storage and retrieval.  This article explains the need biomedical researchers have for managing large amounts of information.  The article provides details of the methodology, procedures, and rules, used to set up searches in SemRep and Semantic MEDLINE, two different search applications.  The authors briefly mention other computer databases, including Metathesaurus, the Unified Medical Language System, SNOMED, and SemMedDB, and the type of information they provide.  Then the authors use Alzheimer’s disease to demonstrate in detail how to conduct a search in the SemRep and Semantic MEDLINE applications.  Finally, the authors summarize how the applications supplement document retrieval, summarization, and visualization of search results for biomedical researchers.  The authors discuss how the search results allow users to explore concepts and relationships within identified citations.

QUESTIONS (True or False)

1. “Biomedical text mining” is a term used to for computer methods which identify relevant information in large volumes of biomedical literature.

2. Semantic MEDLINE generates results in a searchable PDF format.

3 Semantic MEDLINE provides a user with a sense of how many associations have been found in the literature search.

4. A primary mechanism for gaining familiarity with the work of others is through research literature.

ANSWERS

1. T

2.  F - Semantic MEDLINE generates results visually through use of a connected, interactive graph with arcs representing relationships between the relevant subjects identified.

3. T

4.  T

**Stortz et al. Murine Models of Sepsis and Trauma: Can We Bridge the Gap?, pp. 90-105**

Primary Species: Mouse (*Mus musculus*)

Domains 1/ 2: T2, K1

SUMMARY: The most common laboratory animal species used for trauma and sepsis research is the mouse.  The murine model of sepsis and trauma has been used to understand the pathophysiological changes during sepsis and trauma, as well as in the development of life-saving therapeutic agents.  Advantages of using the mouse as a model are numerous and varied, including the ability to use “humanized” mice, high fecundity, abbreviated life cycle, and the widespread availability of mice and reagents.  However, due to fundamental differences between the two species, mice may not be the ideal model (divergence of transcriptomic response, mismatch of temporal response patterns, differences in innate and adaptive immunity, and heterogeneity within the human population in comparison to the homogeneity of the highly inbred mouse strains).  There many models of trauma that mice can be elicited to, and polytrauma models capitulate disease and treatment models the best.  Advantages and disadvantages of sepsis models are described in the article, as well as limitations of the murine models created.

QUESTIONS

1.  The “humanized mouse model” used for translational sepsis research is created using the following technique

a.  Transplanting selective embryonic stem cells from a septic mouse into the embryo of a healthy recipient mouse and allowing blastocyst to develop

b. Allowing the fusion of gametes from two distinct species to form a single zygote

c.  Engrafting human CD34+ hematopoietic cord blood stem cells into gamma-irradiated neonatal NSG mice

d.   By artificially propagating cell lines in the laboratory following the fusion of an NSG embryonic cell with irradiated C57BL/6 embryonic stem cells.

2. Advantages of using murine models for preclinical experiments, including sepsis and trauma, include which of the following?

a.  Mice have a well-characterized genome, with a high degree of conserved synteny between mice and humans

b.  Heterogenic stocks of mice consistently have similar comorbid conditions to that of humans

c.  Laboratory mice are housed in conditions that mimic human health exposures, and therefore respond similarly to treatment options

d.  Mice age at approximately the same rate as humans

3.   T/F:  It is acceptable to deny analgesic support to an injured or septic animal without direct experimental evidence that providing analgesic support would invalidate the experimental results

4. What has been determined to be an acceptable method in which to create polytraumatic models to mimic conditions seen in humans leading to sepsis and trauma?

a. A pendulum dropped from a pre-determined height onto lungs, liver, and the femur bone

b.   Placing a mouse that did not receive analgesic into a circular metal drum and subsequently tumbling the mouse repeatedly

c.   Daily oral gavage of a cecal slush solution followed by blunt force trauma to the liver

d.   Pressure controlled hemorrhagic shock creation, followed by creation of a long bone fracture and associated soft-tissue injury, and laparotomy with cecotomy

5. Which of the following murine models of sepsis is an example of the disruption of endogenous protective barriers?

a. Continuous IV administration of LPS

b. Cecal ligation and puncture

c. Inoculation of live bacteria intravenously

d. Intraperitoneal implantation of a fibrin clot impregnated with viable bacteria

6. What is an advantage of performing colon ascendens stent periotonitis (CASP) as a model of murine sepsis?

a. CASP produces polymicrobial sepsis and diffuse peritonitis

b. CASP is technically feasible and easily performed in neonatal mice

c. CASP reduces hyperdynamic cardiovascular state of sepsis

d. CASP involves a single organism installation which can be selected by the operator

7. T/F: Cecal Ligation Puncture favors inhibition of the adaptive immune response

8. Which mouse strain has prominent TH1-predominant immune responses?

a. BALB/c

b. C57BL/6

c. A/J

d. DBA/2

9. In murine models of sepsis, do male or female mice have an improved survival rate due to hormonal differences?

10. In highly lethal models of murine sepsis, the cause of death is frequently attributed to:

a. Hypovolemic shock, cardiovascular collapse, and pulmonary failure

b. Disseminated intravascular coagulation and subsequent cardiovascular collapse

c. Renal and liver failure

d. Hypovolemic shock

ANSWERS

1. c

2. a

3. F

4. d

5.  b

6. a

7. T

8. b

9. Female

10. a

**Zeiss. From Reproducibility to Translation in Neurodegenerative Disease, pp. 106-114**

Domain 3; T3 TT3.3

SUMMARY: Reproducibility is the ability to duplicate the results of an experiment when it is repeated under slightly different conditions.  Translation is the extent to which animal studies can be generalized to humans.  The challenge with neurodegenerative disorders and translation is the sheer complexity of the disease.  Genetically engineered mice are used to dissect singular biologic phenomena which may be obscured by complex human systems.  This is considered reductionist in method or breaking out individual parts to help explain the whole.  The challenge with this is translating results to more complex systems doesn’t always work.  Cell-based systems are promising for interrogation of basic mechanisms in human disease, but animal models will continue to be used.  In addition to genes associated with individual neurodegenerative diseases, additional cellular process such as synaptic function, mitochondrial dysfunction, oxidative stress, and inflammation complicate them.  Transferring the traditional understanding of face, construct, and predictive validity from individual models to the body of experiments that demonstrate translatability can combine individual reductionist experiments and improve generalizability.  For a given therapeutic, demonstration of efficacy across models that capture different aspects of the cellular process provide greater support for translation to humans.  Animal studies may be exploratory or therapeutic in nature and both depend upon study design to promote rigor and reproducibility.

QUESTIONS

1. What is reproducibility in the context of scientific experiments?
2. What is translation in the context of animal studies?
3. What does “reduction method” refer to?

ANSWERS

1. Reproducibility is the ability to duplicate the results of an experiment when it is repeated under slightly different conditions.
2. Translation is the extent to which animal studies can be generalized to humans.
3. Reduction method is the breaking out individual parts to help explain the whole.

**Hewitt et al. Accelerating Biomedical Discoveries through Rigor and Transparency, pp. 115-128**

Domain 3: Research

SUMMARY: The concepts of rigor, reproducibility, bias, transparency, and translatability in animal research have received significant attention in the past five years because of concern by the public and scientific communities in the conduct of “low-quality research”, coined when published findings are “unreproducible”. Low reproducibility results from a variety of factors, including specialized experimental techniques/expertise, lack of recognition and/or reporting of confounding variables, inability to recognize or mitigate bias, and confused identification or validation of experimental compounds. These concerns have spurred the development of journal editor guidelines and multiple NIH notices and policy to address scientific training, experimental design, results reporting, and grant reviews in these areas. The NIH Policy on Enhancing Reproducibility through Rigor and Transparency emphasizes the need for scientific rigor to ensure meaningful results are obtained and robustly reported, the assurance of appropriate scientific premise of the proposed work and associated preliminary/prior studies, the authentication of key resources such as cell lines, antibodies, and other biologics, and the evaluation and/or recognition of relevant biological variables such as sex, age, and comorbidities. New grant review requirements (NIH NOT-OD-16-011) take these four issues into consideration and must be addressed in funding applications. A variety of free resources continue to be developed to assist and train scientists for success in scientific rigor, with required instruction in rigor and transparency forthcoming for federally-supported training programs. Thorough methods reporting, from design to conduct to data analysis, and a willingness to share original data will pave the way for success in addressing these challenges in animal research.

QUESTIONS

1. Define scientific rigor.

2.   Define scientific premise.

3.  Which of the following does not define a key chemical resource?

a.  Must be generated with federal funds

b.   May differ from laboratory to laboratory over time

c.  May have qualities and/or qualifications that could influence the research data

d.   Integral to proposed research

4.  True or False. Genetically modified animals are considered key biological resources and do not require authentication.

5.  Confirmatory research \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

a.  Minimizes type II error

b.  Minimizes type I error

c.  Generates hypotheses and models

d.  Allows for less rigor than exploratory research

ANSWERS

1. “Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results.”

2.  “Scientific premise is the rigor, or strength, of the key data supporting the proposed research.”

3.   a. Key resources may or may not have been generated with NIH (federal) funds

4.  False – As a key biological resource, genetically modified animals must be authenticated.

5.  b

**Everitt and Berridge. The Role of the IACUC in the Design and Conduct of Animal Experiments that Contribute to Translational Success, pp. 129-134**

Domain 5: Regulatory Responsibilities

SUMMARY: Reproducibility and clinical translatability are central to the scientific value of animal studies in biomedical research. Institutional Animal Care and Use Committees (IACUCs) are mandated by the Animal Welfare Act and under Public Health Service Policy to assure the ethical and humane use of research animals in experiments conducted in the United States. Due to this mandate, the IACUC is well positioned to help nurture an institutional culture of optimized animal use; the IACUC must consider the scientific aspects of animal experiments to the extent necessary to understand how the animal models proposed are likely to contribute to the accomplishment of the research aims. In addition to fostering a culture of humane care for research animals and a culture of working with the concepts of the 3Rs (refinement, reduction, replacement), the IACUC can help foster a culture of optimized animal use that encourages high quality reproducible studies that contribute to translational success. In part this is achieved when the IACUC is successful in encouraging interdisciplinary collaboration early and often within the animal use community it serves. A well-functioning IACUC should strive to nurture an institutional culture that places value in enhancing the scientific quality of research to help assure the reproducibility of animal studies and translational success of animal models. This is integral to both high quality science as well as excellence in the supporting animal care and use.

QUESTIONS

1. The “scientific 3Rs” are: \_\_\_\_\_\_\_\_\_\_, \_\_\_\_\_\_\_\_\_\_, and \_\_\_\_\_\_\_\_\_\_.

1. \_\_\_\_\_\_\_\_\_\_ refers to the strength of an animal model to remain unaffected by minor variations in test conditions that may occur over the course of experimentation in a single laboratory.
	1. Relevance
	2. Robustness
	3. Reproducibility
	4. Refinement
2. The Federation of American Societies for Experimental Biology have called on IACUCs to promote awareness of published voluntary guidance, such as ARRIVE guidelines and ILAR guidelines for describing animal research in reporting and publications. What does ARRIVE stand for?

ANSWERS

1. Relevance, robustness, and reproducibility
2. b
3. Animal Research Reporting In Vivo Experiments (ARRIVE)