Should IACUCs Review Scientific Merit of Animal Research Projects?

Michael D. Mann, PhD, and Ernest D. Prentice, PhD

Whether IACUCs should review animal research protocols for scientific merit is not addressed in the federal regulations, resulting in ongoing confusion on the subject. The authors examine this issue, discuss the pros and cons, suggest how IACUCs can go about reviewing protocols for scientific merit, and question what effect recent changes in regulations will have on this issue.

Mann is Professor and Executive Chair, IACUC, and Prentice is Associate Vice Chancellor for Academic Affairs, Regulatory Compliance, University of Nebraska Medical Center, 987830 Nebraska Medical Center, Omaha, NE 68198-7830. Please address correspondence to Mann at mman@unmc.edu.

In 1992, Prentice *et al.*[1] asserted that "One of the most contentious issues facing each federally mandated institutional animal care and use committee (IACUC) is scientific merit review." It might seem from the dearth of recent discussion in the literature that this is no longer the case. However, our experience with investigators and even members of the University of Nebraska Medical Center (UNMC) IACUC suggests that it remains an issue. The institution of "just-in-time" reviews for research using animals by the Public Health Service (PHS) and other granting agencies prompts a re-examination of this issue.

Scientific Merit

The dictionary entry for "merit" yields a definition for scientific merit: of scientific worth, scientific value, or scientific excellence[2]. As pointed out by Prentice *et al.*[1], Gordon[3] further clarified the meaning of merit (as referred to in NIH grant applications): "The research should be based on a significant hypothesis and, if possible, oriented towards uncovering an important biological mechanism. Typically, a valuable hypothesis gives insight towards a better understanding of normal physiology, biological mechanisms, disease process, or the prevention or treatment of a disease or injury. The hypothesis should be testable (proved or disproved) by the proposed experiments." According to Donnelly[4], assessment of scientific merit has two parts: "the scientific, human, and social significance of the proposed use" and "how carefully crafted and likely to yield the data required the protocol design is." Similarly, Prentice *et al.*[1] suggested two levels of merit research: the fundamental level and the knowledge-based level. This subject will come up again later.

Responsibility for Scientific Merit Review

Who bears the responsibility for assessing the scientific merit of research projects? Clearly, the funding agency, through study panels or individual grant reviewers, has that responsibility. Donnelly[4], however, stated that "... IACUCs have the duty to question, if not evaluate this merit." This is an opinion that is not shared by everyone. For example, in a sample of three IACUCs from Tufts University, Graham[5] found that 14% ($n = 3$) of the members believed that assessing scientific merit is not a role of the IACUC. In contrast, half of the participants in the study considered the opinion of the IACUC to be the most important component of assessing scientific merit, whereas fewer than a fourth said that the peer review done by the funding agency is most important. Not surprisingly, more than three-fourths agreed or strongly agreed that scientific merit should be more diligently assessed if animals will experience more than slight pain during the research. In an earlier study, Borkowski *et al.*[6] found that 35% of 477 IACUC Chairs "indicated that assessing scientific merit was not an IACUC responsibility." In contrast, 32% "received assurance of scientific merit of a project from non-IACUC personnel, and 18% had established a committee to review scientific merit for internally-funded projects."

However, these are opinions or actions based on opinions. Are there any legal or regulatory precedents for IACUC review of scientific merit? As summarized by Prentice *et al.*[1], there are no unequivocal statements in either the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*)[7] or the Animal Welfare Act[8] (AWA) or Regulations[9] (AWAR) that address assessment of scientific merit. The following

quotations shed some light on this issue:

> Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society[10].

Black[11] argued that relevance cannot be equated with scientific merit. According to him, relevance "implies that the outcome of the research, positive or negative, will have some impact on human or animal health." He states that merit "is a much more ephemeral issue that may or may not include a test for relevance within its context." However, it is not clear to us that relevance is independent of scientific merit, as he uses the terms. How can a poorly designed experiment have relevance? In other words, we would argue that to judge relevance (one of the charges to the IACUC by the PHS *Policy*), the IACUC must look at and judge experimental design and therefore scientific merit[12].

> The animals selected ... for a procedure should be of an appropriate species and quality ... to obtain valid results[10].

> The number of animals selected ... should be the minimum required to obtain valid results[10].

The IACUC is required to review and approve the species and number of animals requested as appropriate to obtain valid results, but how can this judgment be made unless the design of the experiments is examined and approved?

> Procedures with animals will avoid or minimize discomfort, distress, and pain to the animals, consistent with sound research design[13].

> Application and proposals ... shall contain ... a description of procedures designed to assure that discomfort and injury to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research...[14]

> Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative...[10]

Although the *Policy* refrains from the use of the term scientific merit, it seems to us that in these passages it is to scientific merit that it refers.

> Procedures that may cause more than momentary or slight pain or distress to the animals will be performed with appropriate sedation, analgesia, or anesthesia, unless the procedure is justified for scientific reasons...[15]

What scientific reasons could there be for withholding otherwise appropriate sedation, analgesia, or anesthesia? Perhaps the agents that are normally used for these purposes are not effective in these animals. It is more probable that the agent produces some effect, apart from sedation, analgesia, or anesthesia, that might compromise the interpretation of the results of the experiments. In the latter case, the reason is firmly embedded in the scientific design, which the IACUC must understand and accept to approve the exception.

The animal welfare division of the NIH Office for Protection from Research Risks (OPRR, which is now called the Office of Laboratory Animal Welfare, OLAW) did issue a more direct statement in response to the question: "To what extent, if any, is the IACUC responsible for assessing the scientific merit of proposals it reviews?"

> Peer review of the scientific merit of a proposal is considered to be the purview of the PHS funding component, acting through an initial review group (IRG). The PHS *Policy* requires the funding component to verify that the IACUC has reviewed and approved animal activities before the PHS awarding unit makes an award. Additionally, the IRG has the authority to raise specific animal concerns. The primary focus of the IRG is scientific merit, whereas the primary focus of the IACUC is animal welfare. It is evident, however, that there is some overlap of function between the two bodies.
>
> Although not intended to conduct peer review of research proposals, the IACUC is expected to include consideration of the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals in Testing, Research, and Training* (PHS *Policy*, P. 27) in its proposal review process. Principle II calls for an evaluation of the relevance of a procedure to human or animal health, the advancement of knowledge, or the good of society. Other references (sections IV.C. 1 and IV.D. 1) include language such as "consistent with sound research design," "rationale for involving animals," and "in the conduct of scientifically valuable research," which presumes that the IACUC will consider in its review the general scientific relevance of the proposal. The presumption is that a study that could not meet these basic tests would be inherently invalid or wasteful and, therefore, not justifiable[16].

Here OPRR clearly endorses scientific merit review by IACUCs, but it seems with limitations. It is not clear to us how one does a partial scientific merit review.

The USDA has also refrained from using the term scientific merit. However, some quotations from the AWARs and USDA policies may help to illustrate its position on this issue.

> A proposal ... must contain a rationale for involving animals...[17]

> A proposal ... must contain ... identification of the species ... and a rationale for the appropriateness of the species[18].

> A proposal ... must contain ... the approximate number of animals to be used ... and a rationale for ... numbers of animals to be used[18].

All sorts of rationales are possible, but only those that are scientific would be meaningful in this context. A rationale based on experimental design, including data analysis, would be most meaningful. It is difficult to see how the IACUC could review and approve the rationale without

reviewing and approving the scientific design and plan for data analysis.

> Alternatives ... include ... methods that reduce the number of animals to the minimum required to obtain scientifically valid data...[19]

> A proposal ... must contain a description of procedures designed to assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research...[20]

If research is scientifically valid and valuable, then it has scientific merit. These statements seem to suggest that the USDA is assigning review of merit in research to the IACUC, but then the preamble to the regulations says:

> We added the term "animal care and use procedure" or "ACUP" in the revised proposal in lieu of "protocol" to avoid any misunderstanding or implication that APHIS intends to become involved in the evaluation of the design, outlines, guidelines, and scientific merit of proposed research...[21]

The USDA appears to be uncertain about IACUCs judging scientific merit.

Despite the statements of regulatory agencies, it strikes us that there are circumstances in which IACUC review of scientific merit is mandatory, that is, when there is no scientific merit review external to the institution. Prentice *et al.*[1] pointed out that institutional review of scientific merit is particularly important for situations in which an investigator, using in-house funds, initiates a research project for which the review is pending at the NIH, perhaps to obtain preliminary data for a proposal. There may be other types of projects that use external funds obtained without peer review, particularly those investigator-initiated projects sponsored by industry in which unbiased peer review is typically absent. The UNMC IACUC applies the same review process to all research projects using vertebrate animals independently of their funding source. Thus, scientific merit review is conducted on research funded from in-house or from non-peer-reviewed external sources as it is on all other research, independent of funding source.

Arguments Against IACUC Review of Scientific Merit

Clearly, from our previous paper[1], we support the review of scientific merit by IACUCs, but there are arguments against this policy. The following is a discussion of those arguments.

Lack of Proper Expertise

It is true that no IACUC is likely to have members who have expertise in every possible specialty area of scientific investigation. Prentice *et al.*[1] pointed out that a lack of expertise in the precise scientific field of research is not a reason for the committee to ignore merit review. By asking proper questions, a reasonable merit review can be conducted, and, if the protocol involves particularly complex issues or requires expertise beyond that represented on the committee, the IACUC may invite outside consultants to assist in the review. Indeed, this assumed lack of available local expertise may be a primary underlying reason that the USDA and PHS sometimes seem internally conflicted on the role of the IACUC in scientific merit review (see earlier discussion). Black[11] complained that doing so "would increase delay and costs of research considerably, while reducing its timeliness and eventual relevance." Undue reliance on external reviewers might eventually increase delay and cost, but there is, in general, no need to use external reviewers excessively if an IACUC is properly constituted. In more than 17 years of existence, the UNMC IACUC has called upon external reviewers only a few times.

It is interesting that this objection to IACUC review of scientific merit is repeatedly voiced. However, we have frequently heard investigators complain that particular NIH study sections lacked expertise in particular areas of research (in particular the area addressed by their grant proposals). Yet, no one suggests that study sections stop reviewing proposals for scientific merit.

Infringement of Academic Freedom

Steneck[22] states that "[i]t sets questionable precedents to have a single university committee, without any provisions for review, as the source of authority for decision making about research protocols." As support for his concerns, he cites the requirement by the PHS and USDA that institutional officials be prohibited from approving protocols that the IACUC has disapproved. At first glance, this might seem to be a situation without provisions for review, but it must be remembered that the members of the IACUC are appointed (and presumably can be removed) by the CEO (or a designee) of the institution. That in itself is a kind of review—the most powerful kind.

Black[11] also complained that IACUC review of scientific merit constituted at least a threat to academic freedom. He points out that external peer review groups such as NIH study sections "take great pains not to plan or redirect proposed research when reviewing its merit." The implication is that the IACUC, by its nature, somehow does not. First, it seems probable that Black has not had enough experience with the NIH study sections if he believes that. Second, the UNMC IACUC, with which we are most familiar, goes to great pains not to rewrite research protocols for investigators. More often, it interacts with investigators by asking questions designed to encourage the investigators themselves to re-examine their protocols.

As pointed out by Prentice *et al.*[12], "Freedom, be it academic or other, does not imply license under any guarantee of the constitution ... quite simply put, investigators can no longer operate in relative autonomy in an environment devoid of any comprehensive system of checks and balances. Indeed, as we point out in our paper, the local institution now bears the ultimate legal responsibility for the research conducted within its walls."

Diverted Resources

In his critique of the role of IACUCs in the daily care of animals and the monitoring of responsible use, Steneck[22] listed diverted resources as a reason for IACUCs not to be involved. The process is too expensive, and there are not enough funds added to research budgets to cover the costs. Presumably, one could cite this reason to oppose IACUC review of scientific merit. However, multiple layers of review are common in other components of research proposals. For example, departmental, college, and other institutional officials all carefully review budgets and personnel commitments. Using more than one layer of review can actually act as an enhanced safeguard in many areas.

The granting agency is supposed to review scientific merit, and they are already doing it; therefore, one could argue that it is a waste of IACUC members' time to duplicate the review, and it is a waste of experimenters' time to respond to IACUC concerns about merit. Still, one must not forget about the research that is done without peer review; someone must review the merit of such projects. It is also doubtful that the PHS or USDA would endorse this argument against IACUC reviews. Both agencies hold the IACUC to reviewing animal welfare concerns of research. At the same time, the PHS requires the study sections to review these same animal welfare considerations, as evidenced by the existence and recent enlargement of emphasis on Section F of the PHS grant form. Above all that, it is not worth the time and expense if the welfare of animals and the quality of research is not improved by having IACUCs review scientific merit.

Disproportionate Power

Black[11] concludes that "[t]here is a profound difference in the consequences of external and internal review of research." External review (*e.g.*, by NIH study sections) may result in a lack of funding, but the investigator may still pursue alternate funding and still be able to complete the research. A negative internal review by the IACUC effectively prevents the research from being conducted at all. Our opinion is that it was the intention of the regulatory agencies that the institution take full responsibility for all of the research conducted within its jurisdiction. It is the institution that should say, "We will not do this kind of research." The funding agencies do not have that power. They may only say, "We will not fund this kind of research."

How to Review Scientific Merit

Most IACUCs use some kind of form to initiate review of research using animals. The UNMC IACUC ensures that animal research protocols have an acceptable level of scientific merit by asking investigators to respond to a number of questions. The six points of information that address merit evaluation include scientific objectives (aims) of the research; potential value of the study with respect to human or animal health, the advancement of knowledge, or the good of society; justification of the species selection; justification of the number of animals requested in reference to experimental design; procedures to be carried out on live animals and endpoints of animals participation in the study; and investigators' qualifications to carry out the research.

Prentice *et al.*[1] identified two different levels of review of scientific merit: the fundamental and the knowledge-based. At the fundamental level, all scientific members of the IACUC should from training and experience be able to make basic judgments about the adequacy and appropriateness of the experimental design: the testability of the hypothesis, use of controls, sample size, statistical analysis, and the qualifications of investigators. Prentice *et al.* contended that "any trained biomedical scientist with an understanding of scientific methodology can judge the merit of a protocol at the fundamental level, given adequate responses to questions about the six points above." It is the responsibility of the investigator to provide clear and sufficient information to make this judgment. Judgments at the knowledge-based level do require expertise because they involve an evaluation of the particular special method used and of the scientific importance of the study. It is at this level that external reviewers may become necessary participants in the review process. The practice of assigning primary review responsibility based on the scientific expertise of the reviewer addresses this level of review. It is the job of these primary reviewers to consult the literature if necessary and to present, clearly and succinctly, the merits of the proposed research for evaluation by other members of the committee who do not have expertise in the same area of research.

Cost-Benefit Analysis

Orlans[23] asserted, "... I believe it is impossible for an ACUC to do its job without weighing the significance of expected results against the potential harm to be inflicted on the animal." Prentice *et al.*[1] also asserted that justification of a research project cannot be based solely on the existence of a valuable, testable hypothesis. We believe that there are some research projects that should not be done despite the importance of the hypotheses being tested or the potential value of the results. Institutional Review Boards (IRBs) regularly do cost-benefit analyses in reviewing proposals for research using human participants. They weigh the scientific merit of the research, including its purpose, significance, and design. Then they evaluate the costs, that is, potential harm to the participants. When these costs and benefits are applied to the pans of an ethical balance, tipping in favor of benefits allows the research to proceed, whereas tipping in favor of costs precludes it.

It is not clear to what extent IACUCs conduct similar cost-benefit analyses. In reviewing the discussions of the committees, one often sees evidence of such analyses, but it is seldom done overtly. Galvin and Herzog[24] asked undergraduate students to act as an IACUC in reviewing five protocols. The investigators concluded that "[t]he most common theme in the narratives reflected a process in which the participants weighed the potential benefits of

the research with its costs. Usually, these analyses were couched in terms of the suffering of animals pitted against the potential rewards for humans." Among the major categories of decision-making themes in the Galvin study were issues related to the structure of the research, including "experimental design, the potential application of the results to human problems, and the motivations of the researchers." So, they were evaluating scientific merit. One person commented, "There are too many flaws in this idea, so how can conclusions be drawn?" Students were also more likely to reject experiments they thought would fail.

Benefits

What sorts of benefits are acceptable? Participants seek medical, educational, and scientific benefits. In the Galvin and Herzog study[24], some stated that any potential benefit to humans, including non-applied research, justified the use of animals. Others demanded direct applicability to human problems. Some subjects considered research justifiable only if it applied to people and their problems; others considered it justifiable only if it was of direct benefit to other nonhuman species.

Costs

In the Galvin and Herzog study[24], both long-term and immediate costs were weighed: "Immediate costs included pain, harm to animals, and financial costs associated with research." Different individuals would accept or reject different levels of any of these variables: "Long-term costs of the research included the quality of life of animals after the experiment was completed and their ultimate fate." Sometimes the costs of research are too high. Both the PHS and USDA have said that conducting research on paralyzed, unanesthetized animals is unacceptable; the costs in terms of potential animal suffering are too great regardless of the benefits of the research.

Just-in-Time Review

In 1992, Prentice *et al.*[1] quoted a personal communication to the effect that the institution cannot defer scientific merit review to the NIH, that approval of "a proposed activity, conditioned on successful peer review by the NIH is not in keeping with the PHS Policy requirements." As of October 2002, the NIH adopted a 'just-in-time' process for submission of IACUC approval of a research proposal. Using this process, institutions may defer notification of IACUC approval until it is determined that the proposal qualifies for an award and that the award may be made, that is, until after the study section has reviewed and scored the proposal in or near the funding range. At first glance, it might appear that the NIH has removed any requirement or incentive for IACUCs to do scientific merit reviews. However, according to the NIH:

> NIH peer review groups will continue to address the adequacy of animal usage and protections in their review of an application, and will continue to raise concerns about animal welfare issues. However, in no way is peer review intended to supercede or serve as a replacement for IACUC approval. An institution that elects to use IACUC "just-in-time" bears the responsibility for supporting the role of the IACUC[25].

It is clear from this passage that the NIH expects the IACUC to continue to review protocols and proposals as they have in the past. That is, scientific merit reviews by the IACUC should continue.

The advent of just-in-time raises an interesting question: When IACUC review occurs after submission to the NIH, what will be the consequence of IACUC-required modifications in the protocol? It is clear that the NIH wants the institution to communicate such requirements:

> The existing PHS Policy requirement that modifications required by the IACUC be submitted to the NIH with the verification of IACUC approval remains in effect, and it remains the responsibility of institutions to communicate any IACUC-imposed changes to NIH staff[25].

It remains unclear what effect the required changes will have on the proposal's approval. Will the NIH reconsider such proposals when the modifications are substantive, or will the changes simply be entered into the file of the grant? What about the IACUC review that results in a refinement to the protocol, which, in turn, will reduce animal pain and distress but also requires an alteration in the experimental design—for example, the experiment is not as "tightly controlled?" How will the NIH respond to an IACUC-mandated redesign of an experiment? To pursue this issue further, how will the NIH respond to an IACUC review that mandates an expensive live animal replacement, which cannot be accommodated by the budget in the grant proposal? Will the NIH reconsider the funding level? Finally, what about the reaction of an investigator who receives notification of funding from the NIH but finds that the IACUC either does not approve the research or mandates changes that either delay the award or kill it? This potential conflict is not unique to the IACUC. The institution or state legislature can restrict the kinds of research conducted by the institution regardless of the source of funding, merit review outcome, or IACUC approval. These are just a few of the thorny questions that could arise when the IACUC does not cede its authority and responsibility for review to the NIH.

Conclusions

It is clear that scientific merit review by the IACUC is still a contentious issue that warrants continued discussion, particularly in the context of cost-benefit analysis and just-in-time review. The bottom line, however, is that lawmakers and regulatory agencies expect the IACUC to serve as a "gatekeeper" that ultimately ensures that research involving animals is justified and humanely conducted.

References

1. Prentice, E.D., Crouse, D.A. & Mann, M.D. Scientific merit review: the role of the IACUC. *ILAR News* **34(1-2),** 15–19 (1992).
2. *Webster's New Universal Unabridged Dictionary*, 2nd edn. 1127 (Simon and Schuster, New York, 1979).
3. Gordon, S.L. Ingredients of a successful

grant application to the National Institutes of Health. *J. Orthop. Res.* **7(1),** 138–141 (1989).
4. Donnelly, S. in *Animals, Science and Ethics* (eds. Donnelly, S. & Nolan, K.) 8–13 (Hastings Center Report, Briarcliff Manor, CT, 1990).
5. Graham, K. A study of three IACUCs and their views of scientific merit and alternatives. *J. Appl. Anim. Welfare Sci.* **5(1),** 75–81 (2002).
6. Borkowski, G., Hunter, A., Field, K. & Sischo, W.M. Institutional animal care and use committees: a survey covering 10 years of experience. *Contemp. Top. Lab. Anim. Sci.* **36(5),** 42–45 (1997).
7. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986).
8. Animal Welfare Act. 7 USC 2131 et. seq.
9. USDA APHIS. 9 CFR Parts 1 and 2.
10. Interagency Research Animal Committee. *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training* (Office of Science and Technology Policy, Washington, DC, 1985).
11. Black, J. More on IACUCs and merit review. *ILAR J.* **35(1),** 1 (1993).
12. Prentice, E.D., Crouse, D.A. & Mann, M.D. To the editor. *ILAR J.* **35(1),** 2–3 (1993).
13. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* IV.C.I.a (US Department of Health and Human Services, Washington, DC, 1986).
14. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* IV.D.I.d (US Department of Health and Human Services, Washington, DC, 1986).
15. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* IV.C.I.b (US Department of Health and Human Services, Washington, DC, 1986).
16. Office for Protection from Research Risks. The Public Health Service responds to commonly asked questions. *ILAR News* **33(4),** 68–70 (1991).
17. USDA APHIS. 9 CFR 2.31(e)(2).
18. USDA APHIS. 9 CFR 2.31(e)(1)(2).
19. USDA. *Animal Care Policy Manual*. Policy #12: Consideration of Alternatives to Painful/Distressful Procedures. (21 June 2000).
20. USDA APHIS. 9 CFR 2.31(e)(4).
21. USDA APHIS. 9 CFR Part 1(Preamble).
22. Steneck, N.H. Role of the institutional animal care and use committee in monitoring research. *Ethics Behav.* **7(2),** 173–184 (1997).
23. Orlans, F.B. Research protocol review for animal welfare. *Invest. Radiol.* **22(3),** 253–258 (1987).
24. Galvin, S.L. & Herzog, H.A. The ethical judgment of animal research. *Ethics Behav.* **2(4),** 263–286 (1992).
25. NIH. DHHS. Amended policy statement. Laboratory animal welfare: change in PHS Policy on Humane Care and Use of Laboratory Animals. *Federal Register* **67(152),** 51289–51290 (7 August 2002).

Hosting a

meeting?
conference?
workshop?

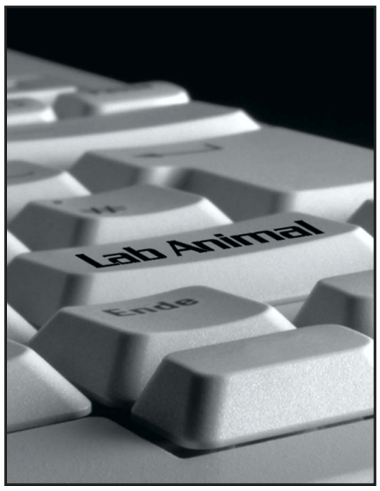
Send listings to:

Lab Animal
345 Park Ave. South
New York, NY
10010-1707

email:
labanimal@natureny.com

Lab Animal

Access
Lab Animal
Online



Your FREE Access to Regularly Updated Features including:

Monthly Columns
Feature Articles
Job Listings/Classifieds

Plus valuable resources for:

Meetings and Conferences
Related Links, By Subject
Search Functions
The Lab Animal Buyers' Guide

www.labanimal.com