Report of the NIH Rat Model Repository Workshop

Table of Contents

FOREWORD

On behalf of the National Institutes of Health (NIH), the National Heart, Lung, and Blood Institute (NHLBI) convened this workshop to develop a plan for a Rat Model Repository. The workshop was designed to plan what is needed by the research community, to recommend how to set up such a repository, to identify the most able group to establish this resource, and to decide how to assess and solve the problem of genetic heterogeneity among members of rat strains.

The NHLBI currently coordinates a consortium of 13 NIH Institutes and Centers to develop important genomic tools and resources for the rat through the Rat Genome Project (genomic libraries, genetic map, radiation hybrid cell lines, normalized cDNA libraries, allele characterization, cytogenetic map) and the Rat EST Project (array and distribute cDNA libraries, produce ESTs from cDNA libraries, and construct a gene-based EST map). The Institute is also providing leadership for NIH to define the parameters and needs required to establish a significant, comprehensive rat database.

As the reagents, information, and materials from these efforts become increasingly available, they will create a significant, increased demand for the available models and will, at the same time, provide the ability to generate new model strains. Hence, it is critical to have a Rat Model Repository for the collection, characterization, standardization, maintenance, development, and distribution of current and future rat strains. In addition, the repository would address a number of other important problems. For example, lack of accessibility is a major limitation to studies using inbred rat models because commercial suppliers carry a very small subset of inbred rat models. Another problem is the lack of quality control and genetic monitoring of the maintained strains. The lack of models of known genetic purity can impede research progress, compromise the value of many studies, and lead to wasteful and inefficient experiments. It is also important to maintain existing strains because they have extensive physiological, pharmacological, and toxicological data sets. Since exact re-derivation of a strain is not possible, their loss would be both scientifically and financially wasteful.

This workshop was structured to enable as much work as possible to be done in advance of the meeting (including the use of a Web site that provided a forum for posting predefined questions and the answers developed by participants) and was designed to promote maximal interaction for the development of implementable recommendations through the Breakout Groups and Plenary Sessions. The report developed by this workshop will be used to guide the NIH in this most important endeavor.

EXECUTIVE SUMMARY

BACKGROUND

This is a time of great opportunity for research utilizing the rat to study biology and disease. Advances in the genome projects, including obtaining the complete sequence of the human genome within the next 3 to 5 years, and the opportunity to create and utilize animal models toward the goal of unraveling the causes of human disease have never been greater. In addition to the rapid expansion of genomic tools, there are methods for ensuring genetic and microbiological quality and new embryological tools that are, or will soon be, available for the rat. Since the rat has many unique features and advantages for use in understanding the biological and genetic bases of health and disease, protection and availability of genetically defined rat models are imperative for the research community. A set of critical needs, including strain standardization, strain preservation, and genetic and microbiological monitoring must be met for the optimal use of rat models of human disease. Fulfilling these critical needs will facilitate the development of an approach for discovery of gene function by linking physiology, genetics, and clinical phenotypes together using comparative mapping techniques, thereby enabling unparalleled opportunities for discovery in biomedical research.

As a consequence, the National Institutes of Health (NIH) Director, Dr. Harold Varmus, asked the National Heart, Lung, and Blood Institute (NHLBI) to convene a distinguished group of national and international scientists. Fifty-eight scientists met on August 19 and 20, 1998, outside Washington, DC, to discuss the needs, use, opportunities, and parameters for optimal importation, standardization, maintenance, and distribution of genetically defined rat models.

RECOMMENDATIONS

To meet the challenges and opportunities of the future, the workshop participants recommended the establishment of a National Rat Genetic Resource Center (NRGRC). This Center should be located in a setting that has a strong research environment and would provide a minimum of 200 well-characterized and standardized rat models. The NRGRC should accept up to 50 new rat strains per year, rederive and cryopreserve all strains, and maintain 44 rat strains as live colonies with a daily census of more than 4,000 rats. The total cost for all activities, including distribution, is $35 million for the first 5 years.

The objectives of the NRGRC would be to serve as a national, central resource that will select, maintain, distribute, and preserve genetically defined rats; to coordinate the extramural NRGRC activities with the intramural NIH Genetic Resource (NGR); to develop a cost-effective central resource that will maintain the maximum number of strains without compromising the quality of strains; to establish criteria of strain selection, preservation, and distribution of genetically defined rats to the

research and supplier communities; to facilitate and implement the establishment of standards for genetic, phenotypic, and microbiological monitoring; to participate in the development of new genetic technologies, e.g., embryonic stem cell production, nuclear transfer, etc., that will improve the function of the NRGRC and be disseminated to the scientific community; to provide relevant information to the scientific community via a Web page that interfaces with other rat databases and to develop a data management system that serves the internal needs of the Center; to institute an Advisory Board to oversee the operation and activities of the NRGRC, to set broad policy guidelines, and to report to the appropriate NIH designee; to provide training to the research community in the various technologies and approaches used at the NRGRC; and to sponsor meetings to discuss various uses of the rat in biomedical research and the developments in rat genetics and genomics.

The staff of the facility should consist of a director with expertise in genetics, several scientific research staff for research and development, informatics personnel, administrative personnel, a facilities manager and facilities maintenance personnel, cryopreservation personnel, animal care technicians, and quality control technicians.

An Advisory Board should be convened to oversee the operations and activities of the NRGRC and report to the NIH its recommendations on implementation, access, and future directions of the NRGRC. This Advisory Board should consist of members with expertise in facility management, genetics, pathology, informatics, and cryopreservation. In addition, the Advisory Board should have a representative from an outside repository and representatives expert in disease models, such as transplantation, cardiovascular, toxicology, cancer, neurosciences and behavior, immunogenetics, autoimmunity, and rat reproductive biology.

BENEFITS

Establishment of the NRGRC will have a broad impact on a wide range of research areas by providing an effective solution to a number of problems and by providing a mechanism that will meet the current needs and anticipated increased demand due to the development of important genomic tools and resources. For example, lack of accessibility is a major limitation to studies using inbred rat models because commercial suppliers carry a very small subset of inbred rat strains. Strains of known microbiological and genetic quality will reduce the problems engendered by the lack of models of known genetic purity, which impedes research progress, compromises the value of many studies, and leads to wasteful and inefficient experiments. Strains obtained from other investigators often have infectious diseases, which can spread to the whole animal house of the recipient. It is also important to maintain existing strains, because they have extensive physiological, pharmacological, and toxicological data sets. Since exact reconstruction of a strain is not possible, their loss would be both

scientifically and financially wasteful. It is also wasteful to maintain live colonies of animals for which there is often only sporadic demand, because few investigators have the technical ability to cryopreserve stocks. The NRGRC will provide the appropriate models that will be used to generate the knowledge of fundamental biological and genetic mechanisms in both health and disease that is needed to develop new diagnostic, prevention, and treatment approaches for human diseases. In an era of discovery where defining function of genes and defining pathways involved in disease are the rate-limiting steps, the rat is likely to remain a major biomedical research model system.

REPORT OF THE
NIH RAT MODEL REPOSITORY WORKSHOP

INTRODUCTION

This is a tremendously exciting time for scientists engaged in research aimed at the alleviation of human disease. With advances in the genome projects, including obtaining the complete sequence of the human genome within the next 3 to 5 years, the opportunity to create and utilize animal models toward this goal has never been greater. In the past 30 years more than 500,000 publications used the rat as an experimental species. The first few decades of the 21st century are likely to be dominated by assigning function to the complete genomic sequence, particularly with respect to those regions involved in common disease. While the paradigm for ascribing function to the genome is not well defined, it is clear that investigators will use comparative mapping strategies and multiple species platforms to accomplish this goal. Toward this end, the rat offers the best “functionally” characterized mammalian model system. In a number of instances, the rat offers a number of unique advantages for modeling human diseases, developing new therapeutic agents, and studying responses to environmental agents. The size of this animal, for example, makes it ideal for physiological manipulations. Several technologies can be applied in any practical way only to the rat, e.g., microdialysis. The rat is the model of choice in neurobehavioral studies and organ transplantation and is the most convenient experimental model of hypertension. Finally, toxicology has traditionally relied on the rat as a test species, and there is an extensive literature of chemical exposure in the rat.

The recent development of genetic and genomic tools for the rat provides an unprecedented opportunity to take advantage of a rich and robust history of experimental studies utilizing the rat to study human disease. Since 1994 the genomic information of the rat has grown at a truly astounding pace. Currently more than 6,000 "anonymous" markers cover the majority of the genome, with many hundreds of known genes also placed within this framework. A genetic map approaching a 1–3 cM resolution, multiple large insert genomic libraries, radiation hybrid (RH) cell lines and the corresponding RH map, greater than 12 normalized cDNA libraries, allele characterization for nearly all genetic markers in 48 inbred strains of rats, and a cytogenetic map all currently exist. There is an ongoing Rat Expressed Sequence Tag (EST) Project developing full-length cDNA libraries, greater than 50,000 ESTs sequenced, and a gene-based EST map. In addition to the genomic tools for the rat, emerging genetic technologies are now being applied to the rat. The production of transgenic rats is routine in many laboratories and several commercial settings. Transgenic rats are being used to study hypertension and neoplasia, among other important public health problems. Collectively these genomic and genetic

tools enable investigators to “walk” between rat and mouse and human using comparative mapping techniques, thereby providing an approach for discovery of gene function by linking physiology, genetics, and clinical phenotypes.

The rat offers significant advantages for functional studies as well as a wealth of scientific literature. Until recently, publications using the rat have outnumbered publications using the mouse by at least two to one. With the advent of homologous recombination in the mouse, the ratio has been reduced to approximately 1.5:1. Publications reporting the use of inbred rats have occurred as frequently as those using inbred mice, even though standardized rat genetic models are not as readily available to researchers. However, the full potential for the rat cannot be realized because many investigators face difficulties in obtaining genetically and microbiologically defined models. Strains obtained from other investigators often have infections that can contaminate the recipient's animal facility. In some cases, genetic quality control programs are lacking or ineffective, and colonies have become genetically contaminated, in some cases repeatedly. These errors have ruined many years of previous research and financial investment. Moreover, there is the constant potential danger of losing valuable strains because of short-term funding problems arising when a single investigator holds the animals. Pressure to have such resources available will only increase in the coming years as additional genomic and genetic tools and critical germline modification techniques, including rat embryonic stem cells and rat nuclear transfer, become available. This pressure will increase further as a primary focus of basic health care research will be to define the function of thousands of genes. Progress in these areas is clear and the future of the rat as a critical species of disease models is very bright.

To best meet the needs of the broad rat research community and to provide the foundation for consistent and well-characterized rat models for human disease, it is imperative to establish a national, central repository resource—a National Rat Genetic Resource Center (NRGRC). The main functions of this repository would be as follows:
(1) Strain standardization, i.e., the repository could maintain core colonies of the most widely used inbred rat strains of high microbiological and genetic quality breeding nuclei, which could be distributed to both investigators and commercial breeders. This would reduce problems currently being encountered as a result of substrain differentiation among colonies that have been separated for several years. (2) Preservation of valuable strains, including transgenic strains, that are being produced in large numbers. The NRGRC could cryopreserve many of these strains efficiently and economically using methodology that is now routine in a few laboratories.
(3) The NRGRC would be a source of genetically and microbiologically high-quality animals. (4) The NRGRC could provide information, advice, and training in the use of genetically defined rat strains. (5) The NRGRC would, by the nature of its work, be a contributor to the research and development of technological advances in cryopreservation, embryo culture, and

animal maintenance. (6) The NRGRC would be charged to serve as a platform for scientific discourse and international cooperation among the community of scientists utilizing the rat as a model system by sponsoring workshops and annual symposia.

The establishment of the NRGRC will have a broad impact on many areas of categorical disease-based research. It will provide solutions to the problems presented above and is designed so as to provide for the current needs of investigators using rat models as well as anticipated increased demand as new genomic tools and new mutant resources become available. Limitations in the current genetic standardization impede research progress, compromise the value of many experiments by reducing their reproducibility, and can lead to wasteful or inefficient experiments. The ability to preserve strains not in great demand at a given time, but whose future value may prove to be great, by cryopreservation with standard microbiological and genetic quality will result in great financial savings in the long run. In short, establishment of the NRGRC will profoundly impact health care science well into the 21st century by providing a reliable source of critical models of common human disease. This resource will facilitate the translation of the wealth of previously published functional data from rat studies to be integrated with genetic and genomic data. This will help accelerate the identification of gene function.

OBJECTIVES OF THE NRGRC

- To serve as a national, central resource that will select, maintain, distribute, and preserve genetically defined rats.
- To coordinate the extramural NRGRC activities with the intramural NIH Genetic Resource (NGR).
- To develop a cost-effective central resource that will maintain the maximum number of strains without compromising the quality of strains.
- To establish criteria of strain selection, preservation, and distribution of genetically defined rats to the research and supplier communities.
- To facilitate and implement the establishment of standards for genetic, phenotypic, and microbiological monitoring.
- To participate in the development of new genetic technologies, e.g., embryonic stem cell production, nuclear transfer, etc., that will improve the function of the NRGRC and be disseminated to the scientific community.
- To provide relevant information to the scientific community via a Web page that interfaces with other rat databases and to develop a data management system that serves the internal needs of the Center.
- To institute an Advisory Board to oversee the operation and activities of the NRGRC, to set broad policy guidelines, and to report to the appropriate NIH designee.

- To provide training to the research community in the various technologies and approaches used at the NRGRC.
- To sponsor meetings to discuss various uses of the rat in biomedical research and the developments in rat genetics and genomics.

Recommendations for the Development of the NRGRC

To serve as a national, central resource that will select, maintain, distribute, and preserve genetically defined rats.

The NRGRC should be a central resource located in a setting that has a strong research environment. The structure must provide a high level of genetic and health quality of research animals to be maintained in a consistent manner. In addition, investigators will be able to obtain from one source many different, well-characterized rat models.

The workshop participants carefully considered minimal numbers of strains to be managed by the NRGRC. However, the purpose of these numbers is more to set the direction and projected costs rather than to set minimums. The participants are interested in having as many strains maintained as possible. It is anticipated that a competitive solicitation for the resource will enable investigators to develop the most cost-effective strategies to maximize the number of strains maintained (cryopreserved and live colonies for distribution) as well as the best way to develop cost-recovery strategies. The NRGRC should have the capacity to provide a minimum of 200 well-characterized and standardized rat models by the end of a 5-year period. The NRGRC should accept at least 50 new rat strains per year, rederive to remove infectious agents, cryopreserve all strains, store aliquots of all frozen embryos or gametes at an off-site facility, and distribute strains to investigators. The NRGRC should maintain at least 44 strains per year as live colonies for distribution with a daily census of more than 4,000 rats (existing breeders, new breeders, and animals for distribution). While the size and structure of the live colonies will ultimately be determined by the investigators subscribing to the NRGRC, it would need to be cost-effective. For example, the 44 strains maintained could be maintained as follows: 10 strains maintained as breeding nuclei (5 breeding pairs), 32 strains (20 breeding pairs) maintained as small expansion colonies, and 2 strains (100 breeding pairs) maintained as large expansion colonies.

To coordinate the extramural NRGRC activities with the intramural NIH Genetic Resource (NGR).

The major role of the NGR is to serve the intramural program at NIH. In addition, the NGR has undergone several reductions in support and size, resulting in the loss of nearly half of its maintained rat strains. Therefore, despite the recognition of the value of the existing resource (approximately 100 cryopreserved strains and approximately 30 strains maintained as breeding nuclei; 5 breeding pairs), there is an urgent need for an additional program to serve the extensive needs of the extramural community. The two programs must be coordinated to

prevent needless duplication. For this report, the participants assumed the NGR would remain at its current number of maintained strains. Any reduction in the intramural program, therefore, would require an equivalent increase in the extramural program to maintain the minimum number of strains.

To develop a cost-effective central resource that will maintain the maximum number of strains without compromising the quality of strains.

Developing the costs for the NRGRC consumed a large portion of the discussions. The Appendix covers the assumptions and costs breakdown: the assumptions were used to derive the first 5-year budget at $35 million in broad terms. The review group for the competitive applications will be charged with selecting the best center, based on a variety of criteria including cost-effectiveness. However, the most important criteria must be the genetic and microbiological quality of the animals.

The total budget cost includes $5 million in equipment and one-time start-up costs, leaving $30 million with an assumed 50 percent indirect cost, reducing the direct cost to $20 million, or $4 million per year direct cost. The major costs involve the rederivation (cesarean section) of all strains and the per diem cost (approximately 4 times the mouse) as well as the cost for developing the initial infrastructure for the resource. A critical aspect of the NRGRC will be to provide animals for experimentation, as well as breeder stocks and cryopreserved embryos, to the widest possible scientific community. Therefore, the NRGRC will serve both as a repository of well-characterized animals and will stimulate the use of the animals as important biomedical models. The participants chose to leave cost recovery to the applicants and the Advisory Board of the selected center. The participants chose not to project costs required beyond the initial 5-year budget. However, it is clear that the NIH must plan to maintain long-term support of the NRGRC for it to succeed. For example, the annual direct costs for the Jackson Laboratory are currently approximately $3.5 to $4 million per year after a long history of serving as a central repository for the mouse.

To establish criteria of strain selection, preservation, and distribution of genetically defined rats to the research and supplier communities.

The history of rat strains used for critical research on human diseases is impressive in its breadth and depth. A large number of strains are producing highly valuable insights into pathogenesis of disease, with major public health implications, including more than 170 inbred strains and many more substrains as well as a growing list of transgenic lines and congenic/ consomic lines. For example, the Maudsley strains (MR, MMR) are widely used in neurobehavioral studies, including locomotion, avoidance, and maze learning crucial in studies of neuroendocrine function and ethanol abuse, as are the four different strains of alcohol susceptible and resistant strains. In addition to their use in studying susceptibility to autoimmune diseases, the F344 and LEW strains

have been used extensively in cocaine/morphine preference studies, in response to cocaine, amphetamine, and morphine, and in studies of the acquisition of cocaine self-administration. Behavioral parameters such as acoustic startle responses, stress responses, and corticotrophin-releasing hormone have also been studied in these strains. F344 has also been used for aging studies, while FBN, BN, and WKY have been used as models of longevity and neurodegeneration. The F344, LEW, and DA strains have been used extensively to study arthritis and a variety of neurodegenerative diseases. In cancer studies, rat strains have proven valuable in mammary tumor studies, particularly with respect to precancerous lesions. F344 rats develop spontaneous leukemia and prostate cancers. Importantly, modifying genes regulating the incidence of spontaneous and induced cancers are robustly available in the rat. The DA rat has also been used as a model system for multiple sclerosis. R16, LEC, and COP rats are mutant for *Grc*, *Atp7b*, and *Mcs* genes, respectively, and modify cancer incidence in liver, breast, and kidney. The Eker rat is an important model of renal cancer and carries a known insertional mutation that, in the heterozygous state, is associated with spontaneous renal cell carcinoma, uterine leiomyoma, and hemangiomas, whereas the homozygous state is an embryonic lethal. The rat is an important source of diabetes models with key strains including BB, LETL in studies of type I diabetes, and Zucker, ZDF, and GK important in studies of type II diabetes. For cardiovascular disease there are seven inbred strains of rats (GH, FHH, LH, Sabra, SHR, SHRSP, SS) that develop different forms of hypertension and susceptibility to end organ damage. A very large number of transgenic strains of rat are now available. These include the renin gene in hypertension, HLA-B27 in autoimmune disease, albumin promoter regulated SV40 in liver cancer, apolipoprotein A1 in lipid metabolism, and many others.

Therefore, important decisions of priorities should be made by the NRGRC. An Advisory Board should be used to help evaluate the case for entry of each strain. The NRGRC staff would screen out candidate strains that are clearly unsuitable, either because they are duplicates of those already maintained or because they are poorly documented and considered unlikely to be of any great scientific value.

All strains accepted into the NRGRC at the recommendation of the Advisory Board will be cryopreserved. Models maintained in the living state must be determined on the basis of demand at any given time.

Selection and versatility criteria for strain selection to be considered by the Advisory Board would include the following:

- Value of the model
- Current demand
- Estimated future demand
- Difficulty of maintenance
- Uniqueness and difficulty of replacement
- Existence and reliability of other sources

There should be a fee-for-service option in which the users pay for the rats obtained from the NRGRC. The nominator of a new strain to be added to the NRGRC should not be charged to have the animals accepted or cryopreserved and should have the opportunity to receive a few breeder pairs without cost as an incentive to contribute. The cost associated with adding a new strain would be covered by charging those requesting the animals for their research for the cost of providing the animals.

Cryopreservation represents a crucial element of any attempt to maintain the genetic integrity of a core of strains and stocks of rats. Cryopreservation by its nature must be done within the NRGRC and be a function of its permanent staff. Beginning in the late 1970s, rat embryos have been successfully cryopreserved and restored using different protocols. At this time, results are similar among these various protocols. These results do not indicate that one procedure is better than another. For example, one can freeze embryos at the two-cell stage (48 h) in "Minitubes" placed horizontally in an alcohol freezer with propanediol as cryoprotectant. There is the two-step method for freezing eight-cell embryos in glycerol. The Jackson Laboratory freezes a later two-cell stage in straws with propanediol as cryoprotectant. They also use the classic slow freezing with 1 M DMSO and found close to 80 percent survival as tested by developing in culture. In general, these procedures vary from 15 to 45 percent recovery efficiency. Certain publications have described a vitrification method for freezing the morula stage. The option to use several protocols in any given case should be available to the NRGRC, and the decision should be in the hands of the staff, with oversight from the Advisory Board. However, there should be standards for the overall level of success of any cryopreservation protocol in terms of the percentage of thawed embryos that develop to pups.

While it is outside the purview of this workshop, there is a clear need to improve the cryopreservation protocols and reagents for rats. The NIH is strongly urged to stimulate additional research into this area, and it is hoped that the NRGRC would play a central role in that research and development effort. Progress in this area would directly translate to reducing costs in the NRGRC by increasing the success rates.

To facilitate and implement the establishment of standards for genetic, phenotypic, and microbiological monitoring.

This NRGRC would participate in establishing and maintaining standards of quality of rat model strains, both genetically and microbiologically. All rat strains maintained at the NRGRC would be fully characterized and documented for their genetic status and their health/infection status.

The possibility of moving pathogens into the NRGRC is a very serious threat to the mission, and, because of this, all animals that are moved to the NRGRC must be rederived by either cesarean section or embryo transfer, regardless of the supposed health status of the incoming animals. Even in clean embryo settings*, Pasteurella*

pneumotropica and *Mycoplasm sp*. are potential threats, although they can be "cleaned" from the embryo by washing the zona pellucida with hyaluronidase.

Live animals should be housed in room or cage barriers and have sterile food, bedding, and water, in so-called barrier facilities. Rederivation by cesarean section or embryo transfer should be used with standard methodology. Embryos should be obtained from antibiotic-treated donors where necessary and transferred to surrogate dams of known health status. The NRGRC should have a quarantine area set up with separate rooms and different containment measures to facilitate rederivation.

Standard microbiological testing should be done using the surrogate dams from embryo transfer. These animals begin with the required health status, and, after the embryo is transferred and develops, they represent the ideal sentinel. It is recommended that the microbiological testing be done in the NRGRC. However, this decision is to be left to the discretion of the Center Director and Advisory Board.

Standardized microbiological monitoring is constantly evolving, and agencies such as the National Research Council and International Council for Laboratory Animal Science are responsible for disseminating current requirements and state-of-the-art methods. Responsible personnel from the Center should go to annual meetings, such as those sponsored by the American Association for Laboratory Animal Science, where these ideas are discussed.

Full strain history, pedigree information, and a genetic profile should be submitted. The methods and strategies for genetic monitoring are established in several settings, e.g., Hannover, Germany, and the Central Institute for Experimental Animals (CIEA), Japan. Current methodology is described in "Genetic Monitoring of Inbred Strains of Rats" (H.J. Hedrich, ed.) and by Mossmann et al. (1998) in *Methods in Microbiology*, vol. 25. Because these methods will change with time, the NRGRC staff will have to pursue assiduously the latest methodology with the oversight of the Advisory Board.

The participants would encourage a mechanism to make available to investigators and commercial suppliers the standardized, quality-controlled reagents for culture media, freezing protectants, microbiological and virological screening, and genetic monitoring (for example, identical primer pairs or probes for screening) developed by the NRGRC.

The selection of sources of strains of rats itself establishes a standardized "reagent." Achieving a consensus on the genetic definition of a given strain will be enormously valuable to the community of investigators using rat models.

To participate in the development of new genetic technologies, e.g., embryonic stem cell production, nuclear transfer, etc., that will improve the function of the NRGRC and be disseminated to the scientific community.

By virtue of the work conducted at the NRGRC, it is likely to be an important source of methodological advances. Many of the technological necessities of maintaining existing stocks and

developing new mutants and models of human disease require the use of state-of-the-art methods. The NRGRC should be an important source of the development, maintenance, and distribution of these methods.

Involvement of the NRGRC in research and development activities is expected to attract the best and the brightest individuals to staff its mission and to ensure the scientific excellence of the Center's activities.

To provide relevant information to the scientific community via a Web page that interfaces with other rat databases and to develop a data management system that serves the internal needs of the Center.

A local database should be developed with different levels of accessibility. The database should include information on strain origin and pedigree, status of the strain (living or cryopreserved), and strain availability. The database should also contain all aspects of the internal operation (data flow/management systems) and management of the NRGRC, including procedures and results, and have links to other related databases. The mechanism of recovery of information by users of the database should be through accessing the Web page for the NRGRC.

To institute an Advisory Board to oversee the operation and activities of the NRGRC, to set broad policy guidelines, and to report to the appropriate NIH designee.

An Advisory Board should be convened to oversee the operations and activities of the NRGRC and to report to the NIH its recommendations on implementation, access, and future directions of the NRGRC. This committee should consist of members with expertise in facility management, genetics, pathology, informatics, and cryopreservation. In addition, the committee should have a representative from an outside animal resource facility and representatives expert in disease models, such as transplantation, cardiovascular diseases, toxicology, cancer, neurosciences, behavior, immunogenetics, autoimmunity, and rat reproduction. This committee should meet two times a year and as necessary by electronic means.

The Advisory Board should perform a number of important functions, including:

- Making final recommendations on model selection for the NRGRC
- Making recommendations on budgetary allocations
- Ensuring and reviewing quality control implementation within the NRGRC
- Assisting in long-range planning for NRGRC functions
- Nominating *ad hoc* members with special expertise
- Advising in the nomination of membership of the Advisory Board
- Ensuring adequate staffing of the NRGRC to meet its objectives

To provide training to the research community in the various technologies and approaches used at the NRGRC.

The NRGRC should sponsor workshops at the Center for the purpose of training

the research community to use technologies of interest, which the Center utilizes. In addition, visits could be arranged for qualified persons outside the NRGRC having a legitimate interest in technologies being used in the NRGRC. These include, but are not limited to, cryopreservation, barrier maintenance, and embryo transfer. The NRGRC should also sponsor workshops on technological advances at other institutions or scientific meetings as opportunities arise.

To sponsor meetings to discuss various uses of the rat in biomedical research and the developments in rat genetics and genomics.

The NRGRC should provide a platform for scientific discourse in the form of an annual symposium held in a venue and with an audience that reflects the international nature of the NRGRC's activities.

A meeting of the rat community to discuss themes of common interest is critical to the long-term utility of the rat as an important genetic resource. The meeting would be an efficient mechanism for reporting on new technology for preservation, new models being developed (e.g., congenics, consomics, transgenics, embryonic stem cells, etc.), and other matters of scientific interest. Meetings should be held in conjunction with existing workshops such as the International Workshops on Genetic Systems in the Rat, to be held annually after the next workshop (XIII) in Gothenburg, or the International Cardiovascular Meetings. One advantage to this arrangement is that subgroups, such as the International Rat Genetic Nomenclature Committee, which also meets in association with the Rat Workshops, would then be a part of this symposium. The NRGRC should take the lead in organizing these groups into a common symposium and in publishing a proceedings.

A wide range of issues could be considered, including nomenclature, new resources (e.g., new transgenics/ congenics/consomics/RIs, the status of embryonic stem cells for rat, etc.), improved cryopreservation protocols, and quality control methods (genetic and microbiological). Discussion to reevaluate which strains are on-line and which are cryopreserved would be useful. Consideration of international issues—including international standards of genetic and microbiological quality, import/export restrictions, and methods of transferring strains and stocks between countries—should be undertaken.

IMPLEMENTATION

The group of internationally recognized scientists strongly encouraged the NIH to take this unique opportunity to establish a National Rat Genetics Resource Center. The rat has always been an important animal in biomedical research, and its use is expected to expand dramatically with a paradigm shift toward determining gene function. The utility of the information generated by these investigations would be significantly diminished if the rats used in these studies were not standardized and monitored for their genetic purity and their health status. This is particularly important since much of biomedical research is concerned with the genetic bases of disease. Further,

the study of complex diseases requires ready access to critical model systems and optimal health status of the animals used in order to prevent adventitious events due to ill health, which might confound the experiments. The focus of the implementation of these essential components of research should be a National Rat Genetic Resource Center, which, in turn, could also disseminate information and standardization materials to the scientific community both in the United States and abroad.

APPENDIX

BASES FOR CALCULATIONS

To estimate cost, the participants developed a series of assumptions. These are not designed to set numbers, but rather to illustrate what the NIH and the scientific community will receive for a given investment. We fully anticipate and expect the applicants to develop their own cost estimates and justifications for how the Center will manage the distribution of strains only cryopreserved versus live colonies. After funding, the Center Director and Advisory Board will continue to explore and modify means of maximizing the number of strains maintained.

OVERALL COSTS

First year **$11–$12 million (total costs)**
For 5 years **$35 million (total costs)**

START-UP COSTS **$5 million one-time cost**

Equipment
- Cryopreservation
- Microbiological
- Genetic monitoring
- General (freezers, auto baths, pipettes, etc.)
- Computers for laboratory
- Informatics (hardware and software)
- Cages, racks, etc.
- Cage washers, steam sterilizer
- Isolators (laminar flow units)
- Miscellaneous (surgical equipment, etc.)
- Security systems (environmental controls; computer regulation/monitoring)

Renovations

DIRECT COST PER YEAR **$4 million**

$35 million minus $5 million equipment and renovations = $30 million
$30 million minus $10 million (50% indirect costs) = $20 million
$20 million/5 years = $4 million per year

LIVE ANIMAL COST

For this section, per diem costs were set at $1.50 per day per rat. It is difficult to estimate per diem rates, since the services provided or not provided by this fee vary from institution to institution, and there will need to be a balance between the per

diem costs and personnel costs. Here we assume all genetic and microbiological costs and some personnel costs are within the per diem rate. We have not built in a budget that illustrates the ramp-up but rather averaged the costs over 5 years.

Maintaining breeders per year **$936,950**

At steady state, the minimum number of strains are:

44 strains maintained as live colonies	
10 kept only as breeding nuclei x $5,475/strain/yr	$54,750
32 small expansion colony x $21,900/strain/yr	$700,800
2 large expansion colony x $65,700/strain/yr	$131,400
Rederiving 10 strains per year x $5,000/strain	$50,000

Assumptions for cost estimates:

The 10 strains maintained as breeding nuclei were assumed to be new strains, for which the need had not been established. For this process, we assumed 10 new strains would be added each year and 10 retired to be cryopreserved or transferred to a commercial breeder. We are projecting a cost of $5,000 to rederive a strain. Therefore, 10 strains per year x $5,000 = $50,000 per year

Breeding colony (5 breeder pairs)	$5,475/strain/yr
Small expansion colony (20 breeder pairs)	$21,900/strain/yr
Large expansion colony (60 breeder pairs)	$65,700/strain/yr

Cost associated with maintaining animals for distribution **$1.1 million**

Rats to be sold/distributed incur a per diem charge from weaning until they are sold, distributed, or euthanized. For this estimate, we assumed that the number of animals sacrificed represents the average number of animals per day maintained by the Center's budget, since there is no cost recovery for these animals during the first 5 years. After the first 5 years, the participants anticipate that this category should probably be reduced. However, not producing enough animals to save costs initially will be counterproductive. For this estimate, it was assumed that the daily average number of animals incurring a per diem charge would be 2,052 rats based on 90 percent of the produced animals being distributed. We recognize this is a high figure, but we also estimate that the Director and Advisory Board will not maintain a uniform number of animals for distribution. 2,052 rats x 365 days x $1.50 per rat = $1.1 million.

Table 1. Estimated number of animals generated for distribution for each type of colony

	Rats Generated Annually	Number of Rats Distributed	Interim Sacrifices
Breeder expansion (small)	540	486	54
Expansion (large)	1,620	1,458	162

Table 2. Estimated number of rats generated and distributed by group

	Rats Generated Annually	Number of Rats Distributed	Interim Sacrifices
For 32 strains with small expansion	17,280	15,552	1,728
For 2 strains with large expansion	3,240	2,916	324
Totals	20,520	18,468	2,052

PERSONNEL COSTS (APPROXIMATELY 25% OF DIRECT COSTS) $1 million

The staff of the facility should consist of a Director with expertise in genetics, several scientific research staff for research and development, informatics personnel, administrative personnel, a facilities manager and facilities maintenance personnel, cryopreservation personnel, animal care technicians, and quality control technicians.

CRYOPRESERVATION COSTS PER YEAR $450,000

$9,000/strain to freeze and recover x 50 strains per year

SUPPLY/MISCELLANEOUS COSTS $500,000

Miscellaneous laboratory supplies
Informatics support (hardware and software)
Resources for developing better technologies for cryopreservation, etc.
Office supplies
Telephone charges
Travel for Advisory Board members

Travel for investigators
Training course and meeting costs

Rat Model Repository Workshop

Lansdowne Conference Center
Lansdowne, Virginia
August 19-20, 1998

Agenda

Wednesday, August 19, 1998

Plenary Session One

8:30 a.m.	Introduction and Charge	Dr. Mockrin
8:45 a.m.	Rat History and Background	Dr. Gill
8:55 a.m.	Rat Genome Resources	Dr. Jacob
9:15 a.m.	Rat Nomenclature and Rat Map	Dr. Levan
9:30 a.m.	Overview of Major Strains	
	Cardiovascular/Renal	Dr. Rapp
	Neurobiology/Aging/Mental Health	Dr. Harris
10:00 a.m.	Break	
10:15 a.m.	Overview Major Strains	
	Immunology	Dr. Gill
	Cancer	Dr. Pitot
	Diabetes	Dr. Guberski
	Transgenesis	Dr. Hammer
11:00 a.m.	Existing Repository Programs	
	Europe	Dr. Hedrich
	Japan	Dr. Nomura
	USA	Dr. Rall
	Commercial	
	Charles River	Dr. Balk
	Harlan Sprague-Dawley	Dr. Russell
12:30 p.m.	Lunch	

1:30 p.m.	Jax Strategies for Mouse	Dr. Mobraaten
1:50 p.m.	New Strains-Prospects and Promise	
	Rat ES Cell/Nuclear Transfer	Dr. Iannaccone
	RI Strains	Dr. Printz
	Consomics/Congenics	Dr. Kwitek-Black
	Transgenics/KOs/KIs	Dr. Hammer

3:15 p.m. **Breakout Groups**

Group 1 Strain Selection — Dr. Festing
- Criteria for admission to the repository
- Finding strains
- Criteria for animal distribution (academic/commercial)
- Criteria and number of substrains maintained
- Costs

Group 2 The Repository — Dr. Cork
- Central or distributed resource
- Academic and/or commercial distribution
- Import/export
- Existing strains
- New strains
- Requirements: spf/naf
- Quality control
- Costs

Group 3 Maintenance — Drs. Pakes and Iannaccone
- Cryopreserve or maintain breeding colonies
- Research and development for maintenance and preservation
- Identify key features for standard protocol/back-up for storage (cryopreservation)
- Preservation of strains not selected
- Costs

Group 4 Operations — Dr. Hammer
- Advisory group structure, operation, reporting
- How involved is NIH?
- Advertising/Marketing
- Cost Recovery
- Informatics - Interface with databases
- Costs

6:00 p.m.	Recess	
6:30 p.m.	Reception	
7:00 p.m.	Dinner	
8:30 p.m.	Write up Breakout Group recommendations for handouts in the morning	

Thursday, August 20, 1998

Plenary Session II

8:30 a.m.	Breakout Group Reports	
8:30 a.m.	Group 1	Dr. Festing
9:15 a.m.	Group 2	Dr. Cork
10:00 a.m.	Break	
10:15 a.m.	Group 3	Dr. Pakes
11:00 a.m.	Group 4	Dr. Hammer
11:45 am	Lunch	
1:00 p.m.	Breakout Groups reconvene	

Plenary Session III

2:30 p.m.	Final Breakout Group Recommendations Presented	
	Group 1	Dr. Festing
	Group 2	Dr. Cork
	Group 3	Drs. Pakes and Iannaccone
	Group 4	Dr. Hammer
3:30 p.m.	Summary	Dr. Gill
4:15 p.m.	Adjourn	

ROSTER

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