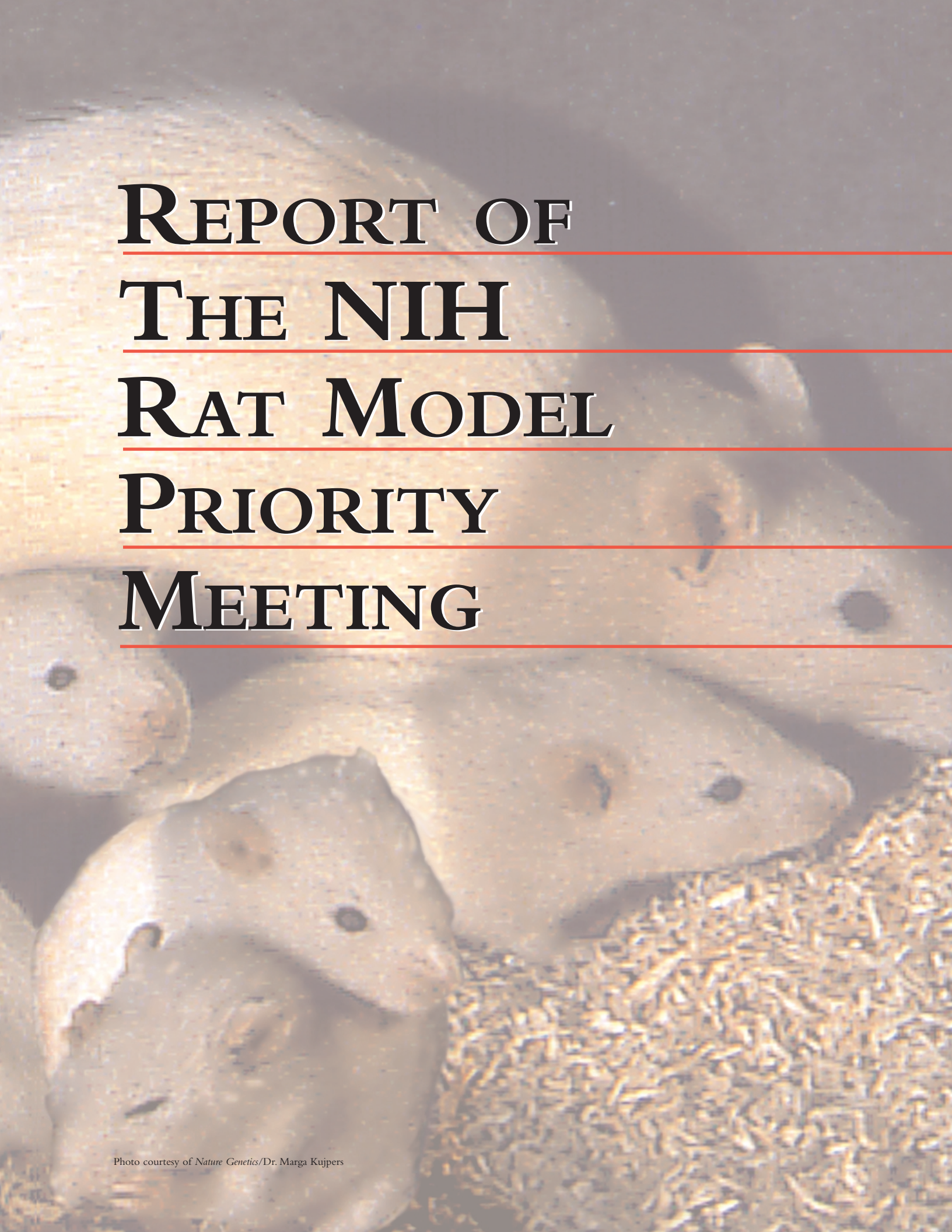
Report of The NIH Rat Model Priority Meeting



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FOREWORD

The National Institutes of Health (NIH), realizing the potential of rat models in understanding basic biology and human health and disease, launched the Rat Genome Program in 1995, followed by the Rat EST Program in 1997. These two programs, which are coordinated by the National Heart, Lung, and Blood Institute (NHLBI), are funded by 13 Institutes and Centers at NIH, and have produced a wide variety of resources. In addition, these programs have begun to provide a powerful tool to link and capitalize upon the data and resources of other model organisms and the human.

We live in an era of extraordinary opportunities and unprecedented scientific discovery. New developments in genomics, genetics, drug discovery, stem cell research, bioengineering, and other fields are creating opportunities for revolutionary changes in the practice of medicine. The purpose of the Rat Model Priority Meeting was to discuss, within this context, the opportunities that rat models offer and the investments that are needed to capitalize on these opportunities. The major issues that were addressed were: where does rat fit in the broader scientific picture, what unique value does the rat model provide, what are the key areas of opportunity for investment, and what will be the impact of these proposed investments. Participants were charged by Dr. Harold Varmus, Director of NIH, to prepare a report that contains a summary of the major themes and recommendations, a sense of priorities, and a practical look at costs.

The 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 provided by the scientific community) and was designed for maximal interaction. The report from this meeting, held May 3, 1999 on the campus of NIH and involving over forty distinguished scientists, can be found on the NHLBI Web site at http://www.nhlbi.nih.gov/meetings/index.htm.

EXECUTIVE SUMMARY

I. BACKGROUND

The rat model provides important strengths for the study of human health and disease. The large number of inbred rat models and the vast amount of data (physiological, behavioral, biochemical, cellular, pharmacological, and toxicological, etc.) provide a superb platform on which to build the genetic and genomic tools and resources to delineate the connections between genes and biology. Importantly, in many instances, the rat is the most appropriate experimental model of human disease.

The National Institutes of Health (NIH), realizing the potential of rat models in understanding basic biology and human health and disease, launched the Rat Genome Program in 1995, followed by the Rat EST Program in 1997. These two programs, funded by 13 Institutes and Centers at NIH, have produced a variety of basic genomic resources. In addition, these programs have begun to provide a powerful tool to link to and capitalize upon the data and resources for both other model systems and the human.

An era of extraordinary opportunities and unprecedented scientific discovery now presents itself. New developments in genomics, genetics, drug discovery, stem cell research, bioengineering, and other fields are creating opportunities for revolutionary changes in the practice of medicine. The rat model must be poised to take advantage of the opportunities available, with suitable investments to capitalize on these opportunities.

As a consequence, the NIH Director, Dr. Harold Varmus, asked the National Heart, Lung, and Blood Institute (NHLBI) to convene a meeting to discuss the opportunities and prioritize the needs to fully take advantage of rat models. On May 3, 1999 a meeting was held on the campus at NIH.

II. NEEDS AND OPPORTUNITIES

Several needs and opportunities were identified, both through the responses to questions posted on the Rat Community Forum (http://goliath.ifrc.mcw.edu/RCF) and at the meeting by the participants. These needs and opportunities were grouped into the two areas of biology/physiology and genomic infrastructure.

A. BIOLOGY/PHYSIOLOGY:

1. Germ-line Modification

The need for access to the germ-line of the rat in order to produce informative mutants is critical. The availability of gain of function (over-expression; knock-in) and loss of function (knock-out) mutations in the rat will be necessary for the functional characterization of genes. Correct assignment of quantitative trait loci (QTL) to genes will require verification from loss of function mutations. Although the production of transgenic rats is now routine, the creation of loss of function mutations (knock-out) or gene replacement (knock-in) by homologous recombination in embryonic stem (ES) cells has not yet been possible in the rat. The gene replacement strategy is essential, as it

provides the means to ultimately study the "natural" mutations that exist within the various rat models of common diseases.

2. National Rat Genetic Resource Center

The genetic integrity of, and access to, important rat strains is maintained by an international effort that depends on the personal good will of many individuals. This effort is inherently inefficient and susceptible to the vicissitudes of funding and local interests. A much more robust approach to the problem of genetic integrity, microbiological quality and distribution of these valuable models would be the National Rat Genetic Resource Center, which was proposed in August, 1998 at the NIH Rat Model Repository Workshop.

3. Rat Genome Database

NIH has issued a request for applications (RFA) for a Rat Genome Database (RGD) to establish a database that will collect, consolidate, and integrate data generated from ongoing rat genetic, genomic, and related research efforts, and to make these data widely available to the scientific community. The applications were due on April 30, 1999 and an award is expected September 30, 1999. The participants strongly endorsed this plan for NIH to implement an RGD.

4. Interaction with the NIH Mouse Mutagenesis and Phenotyping Program

Mutagenesis and phenotyping of rat models, in parallel with the NIH mouse mutagenesis and phenotyping program, will allow significant interaction and collaboration on developing new rodent models, with comparable characterization, of human disease. Random mutagenesis can offer the rat model an alternative to gene targeting strategies, as many of the induced mutations are loss of function. In addition, if rat and mouse mutagenesis and phenotyping programs are established together, each can benefit from the others experience -- the mouse model researchers in biological phenotyping and the rat model researcher in genetic manipulation, as well as the opportunity to compare and contrast the biology between these two model organisms.

5. Strengthening the Rat Model User Research Community

A major success of the meeting was catalyzing the formation of an interactive research community or rat-users. Recommendations to strengthen this research community included the continued use of the Rat Community Forum web site, a series of stand-alone rat genomic/genetic-based meetings, and a number of rat genomic/genetic meetings in conjunction with mouse and human genetics meetings.

B. GENOMIC INFRASTRUCTURE:

1. Rat EST Project (REST)

The REST project has generated more than 93,000 ESTs derived from 12 different normalized cDNA libraries. These normalized libraries combined with a serial subtraction strategy have provided an unprecedented level of

efficiency with respect to identifying unique rat genes, a set of 27,000 Unigene clusters. This is a marked improvement over the 15,000 mouse Unigene clusters generated from more than 300,000 ESTs. However, workshop participants expressed the view that more comprehensive coverage (90%) would offer significant advantages and opportunities by facilitating gene discovery and providing sequence links to the human and mouse genomic sequence. These sequence links will assist the human and mouse communities in assigning gene function by providing connections to the wealth of physiological data in the rat.

2. SNP Discovery and Mapping

The density of markers currently available is nearly an order of magnitude short of the number of markers that will be required to positionally clone genes from the mapped positions. To overcome this limitation, the participants suggested constructing a 3rd generation genetic map using single nucleotide polymorphisms (SNPs) at a resolution of 1 SNP per 100 kilobases. These markers will also facilitate construction of physical map (rough-draft and sequence-ready).

3. BAC Clone Resource

Physical mapping reagents exist that are useful for initiating individual positional cloning projects and are being used by many laboratories around the world. However, with the change in sequencing capacity in both the public and the private sector it is important to consider if these reagents position the rat for the sequencing of its full genome, once the mouse genome is sequenced. Therefore, there is a need to develop a BAC library with 15-fold coverage made from multiple sources of DNA cut using a variety of restriction enzymes or random shear techniques while still maintaining an average insert size greater than 150 kilobases. The currently available BAC/PAC resources have an average insert size less than the optimal 150 kilobases.

4. Genomic Sequence

Within less than two years the sequencing capacity of the publicly funded US and international genomics communities are likely to pass that needed to sequence a mammalian genome to 10-fold redundancy in one year. The rat should be positioned for genomic sequencing immediately after, or in parallel, with the mouse.

III. RECOMMENDATIONS/ PRIORITIES

After a thorough discussion of the needs and opportunities, workshop participants made four major recommendations, which are listed in priority order:

1. **Germ-line Modifications**
   ($8.5 million over 5 years)

Germ-line modification in the rat is critically important to assigning gene function to specific genes and to identifying gene alterations responsible for specific phenotypes. However, germ-line modification in the rat is limited. The highest priority should be to overcome these limitations, thorough the use of the following strategies: (a) The development of nuclear transfer in the rat is an important priority that needs to be met ($5 million over 5 years). (b) The development of dominant negative mutations by pronuclear injection should

be encouraged ($500,000 per year for 5 years). (c) Cryopreservation of zygotes and sperm will help to alleviate the storage and transportation problems ($750,000 over 5 years). (d) The generation of in vitro fertilization techniques in the rat, including intracytoplasmic sperm injection (ICSI), will help the use of cryopreserved sperm by allowing suboptimal sperm to lead to viable offspring ($250,000 over 2 years).

2. Additional Genomic Resources ($30 million over 3 years)

a. EST Development ($2.5 million per year for 3 years)

Participants recommended that the goal of the Rat EST Project be expanded to achieve 90% coverage of all rat genes. Broader coverage will greatly accelerate efforts to identify genes and elucidate their functions in advance of having the complete genomic sequence.

b. SNP Discovery ($6.5 million over 3 years)

Developing a SNP map of the rat is a high priority, as it is required to accelerate the identification of genes (through positional cloning) responsible for complex, common diseases, as well as facilitate the construction of a physical map.

c. BAC Clone Resources ($1 million for 1 year)

Sequencing the rat genome should be placed at very high priority as the third mammalian genome to be sequenced after man and mouse. The key prerequisite for such an effort is a high quality well characterized, and deeply redundant BAC library. This library should have large inserts (average size greater than 150 kilobases), be redundant to a depth of 15-fold or greater, and ideally be produced by more than one restriction enzyme or physical shearing.

d. Pilot Sequencing ($15 million over 3 years)

A complete sequence of the rat genome will provide the critical substrate for understanding the molecular basis of biological function and pathology. A coordinated and systematic approach will be most cost effective. It is however not clear how to optimally sequence the rat given the existence of the sequence for mouse and man, a rich array Unigene models from all three species, and the need to address further genomes. It may be that some form of draft sequence in the rat would strike the best cost/benefit balance. To address this question, a small number of rat genome sequencing pilot studies, each covering a few megabases, should be performed.

3. National Rat Genetic Resource Center ($35 million over 5 years)

Establish this critical resource to maintain and distribute standard rat models as recommended in the NIH Rat Model Repository Workshop report

(http://www.nhlbi.nih.gov/nhlbi/sciinf/model/ratmodel.htm) and also explore creative mechanisms for its maintenance beyond the initial five-year period. With the rich biological and behavior history of the rat model and the upcoming genomic tools and genetic applications, a repository for the large number of current, and future, inbred, transgenic, and congenic strains is a high priority.

4. Interaction with the NIH Mouse Mutagenesis and Phenotyping Program ($1 million per mouse center)

Mutagenesis and phenotyping of rat models, in parallel with NIH mouse mutagenesis and phenotyping program will allow significant interaction and collaboration on developing new rodent models of human disease, with comparable characterization and shared expertise.

IV. BENEFITS

The rat is a principal model organism to link function to genes. The biological relevance and wealth of phenotypic data in the rat, when combined with the current and proposed genomic resources, will provide the opportunity to develop new diagnostic, prevention, and treatment approaches for human health and disease.

REPORT OF THE
NIH RAT MODEL PRIORITY MEETING

I. BACKGROUND

The rat model provides important strengths for the study of human health and disease. The large number of inbred rat models and the vast amount of data (physiological, behavioral, biochemical, cellular, pharmacological, toxicological, etc.) provide a superb platform on which to build the genetic and genomic tools and resources to delineate the connections between genes and biology. Importantly, in many instances, the rat is the most appropriate experimental model of human disease.

The NIH, realizing the potential of rat models in understanding basic biology and human health and disease, launched the Rat Genome Program in 1995, followed by the Rat EST Program in 1997. These two programs, funded by 13 Institutes and Centers at NIH, have produced a variety of basic genomic resources. In addition, these programs have begun to provide a powerful tool to link and capitalize upon the data and resources of other model organisms and the human.

An era of extraordinary opportunities and unprecedented scientific discovery now presents itself. New developments in genomics, genetics, drug discovery, stem cell research, bioengineering, and other fields are creating opportunities for revolutionary changes in the practice of medicine. To facilitate the translation of these discoveries to improved human health, the rat model, which remains a dominant biological discovery tool, must be poised to take advantage of the opportunities available, with suitable investments to capitalize on these opportunities.

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 meeting to discuss the opportunities and prioritize the needs to fully take advantage of rat models. The NHLBI, in conjunction with 18 NIH Institutes and Centers, organized a broad-based meeting of distinguished scientists to identify needs and opportunities, establish priorities, and recommend costs.

II. STRENGTHS

The rat is a principal model organism to link function to genes. The biological relevance and wealth of phenotypic data in the rat, when combined with the current and proposed genomic resources, provide the opportunity to accelerate the development of new diagnostic, prevention, and treatment approaches for human health and disease.

A. BIOLOGY

The rat model has made enormous contributions to our present understanding of biological function and behavior. The rat has been a widely studied model system, as demonstrated by the number of publications in the last three decades (nearly 500,000 PubMed publications). Large numbers of rat disease models exist (more than 250

inbred, congenic, mutant, or transgenic rat strains) to explore disease-related variables. Modeling of human diseases can capitalize on the considerable strengths that these rat models offer to the future of physiological and functional genomics, and in delineating genes of complex diseases. Many of the rat models have already proven their utility for addressing the human condition. Presently rats comprise 28% of laboratory animals (AALAC) and provide important models for cardiovascular, pulmonary, renal, endocrinology, reproduction, toxicology, parasitology, immunology, development of dental plaque and gingivitis, polycystic kidney disease, spongioform encephalopathy, alcoholism, nutrition, cancer, growth, diabetes, autoimmune disease, arthritis, asthma, endocrinology, multiple sclerosis, learning, memory, behavior, and neurological health and disease. In some cases, specific aspects of human disease are recapitulated well only in the rat, making these animals a unique resource for studying and identifying genetic pathways relevant human disease. Many examples exist of biological relevance to human health and disease, and several were presented at the meeting and/or discussed on the Rat Community Forum (http://goliath.ifrc.mcw.edu/RCF/) prior to the meeting. Some examples include:

Cardiac Function and Hypertension: The rat is a model of choice for many physiological studies related to cardiac and vascular function, pulmonary circulation, energetics and metabolism, microcirculation, neural control of cardiovascular, renal and pulmonary function, age and gender related differences, studies of arterial pressure regulation, hypertension, cell and system integrative function, and signal transduction studies. Many inbred rat strains are currently available and well characterized (there are 9 inbred strains for arterial pressure regulation and hypertension alone). An example of the strength of combining physiology and genetics was described. Results were shown in which 220 phenotypes were determined in a large F2 cross between an inbred strain of Dahl S and Brown Norway rats in which multiple cosegregation analyses were performed using 220 “informative markers” that distinguish these two strains. More than 30 regions on 16 different chromosomes were significantly related to measured parameters that are likely determinants of blood pressure. Combining the results from several rat strain crosses and examining the overlapping QTL regions allowed the prediction of the location of several human chromosomal regions that had been previously identified in blood pressure linkage analysis studies in human populations. These results now enable investigators to develop models that share phenotypic similarities to the clinical picture as well as share homologous genomic regions responsible for the similarities, thereby providing unprecedented opportunities for generating new models directly relevant to human disease.

Behavioral and Neuropharmacology of Addiction: There is an appreciable depth of knowledge of rat neuroanatomy and neurophysiology. Complex behavioral procedures involved with drug self-administration and developmental studies related to substance abuse, including the behavioral effects of maternal drug exposure, have been extensively characterized in the rat model. Three levels of biological analysis used in the neurological study of alcohol and drug addiction (Intra-Cellular B signal transduction processes; Trans-Cellular B signal transmission processes; Multi-

Cellular B signal integration processes) all use the rat successfully to model human biology. Rat studies using models of ethanol self-administration are providing important insight as to how alcohol and aggression interact, with data that appear more related to the human situation than the other models systems. One of the most important attempts to understand the lasting effects of drug actions in the brain has been to look for permanent changes in brain function following chronic drug administration, such as the effects in neural sensitivity and function that last after long periods of drug abstinence. These changes are believed central to the issues of drug taking relapse. That drug and alcohol exposure has the potential for epigenetic effects altering gene expression is the basis for several hypotheses as to the mechanism for these lasting effects. These cellular studies in the rat have become the cornerstone for this approach where connections are being developed between cellular function and behavioral phenotype in the rat related to relapse. Gene by environment interactions is a critical area for study in the addiction field. The environmental exposure (light, noise, proximity, etc.) can affect the interpretation of the genetic contribution to several of alcohol's behavioral effects. For instance, environmental factors have major effects on ethanol preference in both heterogeneous and selected rat strains. While this is an understudied area in all model organisms, the studies in rats using complex behavioral self-administration procedures have a high importance, given the availability of the several selected alcohol-preferring rat lines that meet the criteria as a model of human alcoholism.

Arthritis and Related Autoimmune Disorders: Rat models of arthritis and related autoimmune diseases are biologically relevant models to common human diseases such as rheumatoid arthritis, insulin-dependent diabetes, multiple sclerosis, and autoimmune uveitis. More than 200 inbred (e.g., LEW, DA, BB-DP, BB-DR, F344, BN, ACI), congenic (e.g., MHC and other loci), mutant (e.g., athymic nude), or transgenic (e.g., HLA-B27, TNF-alpha, HTLV-1 env-pX) rat strains exist in which to explore disease-related variables. Several important models of adjuvant and bacterial cell wall arthritis are only available in the rat, as rats are naturally more susceptible to these disease models. In addition, disease penetrance in mice (as noted in the necessity for repeated injection of potent "adjuvants" for disease induction) is usually less than observed in rats, complicating genetic analyses. Likewise, there are several unique infectious arthritis models available in rat (e.g., Yersinia enterocolitica and Chlamydia trachomatis arthritis). There are unique examples of gene by environment interactions in the rat (induction of insulin-dependent diabetes in BB-DR rats, and induction of arthritis with low potency, non-immunogenic adjuvants in DA rats) as well as responses to therapeutic agents in rat (rats are responsive to non-steroidal anti-inflammatory drugs, whereas mice are resistant).

Gender-related disease susceptibility profiles in rat are similar to those observed in humans. Female rats are more susceptible (as are humans) to most of the arthritis models than are males. In contrast, male mice are more susceptible than females.

Learning, Memory, and Behavior: The past 100 years of behavioral research using the rat has revealed the complexity of learning and memory, as well as the multiplicity of brain systems that support it. These studies show that a combination of thorough behavioral characterization and neurobiological investigations can provide major insights into the specific brain systems that mediate memory. Continuing efforts that respect the psychobiological character of rats have recently allowed investigations of even more complex cognitive and memory capacities. For example, the rat's superb learning abilities have been exploited using odors as cues and foraging as a modality for behavioral expression. In this format rats show exceedingly rapid learning of simple discrimination problems - acquiring them typically in 1-2 trials and retaining the information for at least several days. With this capacity in hand, rats have been trained using the same methods on very complex problems such a Piaget's transitive inference task, a test solved by human children at about the age of 7. Rats show robust transitivity and this capacity is fully dependent on the hippocampus.

Endocrinology and Reproductive Biology: There are various aspects of rat husbandry that provide attractive features for reproductive physiological work; rat pregnancies are more size consistent (compared to the mouse), rat cycling is relatively non-pheromonal (similar to human), rats can be bred quickly after parturition, and rat brains show early sexual dimorphism.

Respiratory and Pulmonary Biology: Many models of lung disease use rat lungs and/or rat cells. There is a large body of literature in the rat on the neurophysiologic structures, interventions and cardiorespiratory monitoring that enable productive investigation in understanding sleep and breathing. One significant advantage of the rat model is the ability to perform lung function studies. In the rat, sleep, breathing, and cardiac function measurements can be simultaneously recorded. The availability of detailed neurofunctional information (in addition to a history of behavior studies) provides an efficient transition from genes to complex behaviors such as sleep. In addition, the rat model mimics many features of human asthma and acute lung injury. Similar phenotypic measures can be accomplished in the rat and human, and have not proven successful in other model systems.

Toxicology and Pharmacology: Pharmacogenetics is a major emerging research area. Not surprisingly the rat remains a dominant model system for risk assessment of virtually all forms of therapeutics and chemical substances. Insofar as current risk assessment protocols require more than one species it is critical to continue to develop the rat for risk assessment. For example, the acceptance of transgenic animals for risk assessment linked to the increased availability of this technology in rats provides for developing better models systems. Therefore, the combination of classical risk assessment with genetic susceptibility to chemical agents provides unparalleled opportunities for linking the vast databases on drug responses to the genome, as well as increasing our understanding of gene-drug interactions.
Cancer: The rat models for breast cancer are good representations of human breast cancer. They are hormonally

responsive, can be rapidly induced in virus free animals, and their histopathology and premalignant stages of development resemble those of human breast cancer. The great majority of cancer chemoprevention models in use today are rat based.

B. PHENOTYPING

One of the major strengths of the rat model is the in depth characterization and well defined, relevant phenotypic measures. The size of the rat allows many important measures to be quantified, without a delay caused by needing to develop new technologies, including: invasive procedures (intravenous cannulation for drug administration or blood collection, surgical manipulations, nerve recordings, blood pressure monitoring, etc.), chronic measurements (regional blood flows, cardiac output, etc.), collection of tissues (synovium, lymph nodes, pituitaries, retina, heart, etc.), and serial blood collections. In addition, arthritis of individual joints in rats can be precisely described in terms of the day of onset, the pattern of onset, the number and distribution of joints involved, the severity of swelling or inflammation (in mice, since the joints are so small, descriptions are usually limited to gross descriptions of swelling of whole digits or entire feet). The general metabolic rate in mouse is approximately 3 times that of the rat and, therefore, issues of the duration of drug action and dose are a problem when studying addiction processes in the mouse. The absolute dimensions of the rat has advantages for some studies, such as the use of multiple electrodes and transducers, or the injection of neuroanatomical markers, where lack of resolution through diffusion seen in a smaller brain is not a problem in the rat. All of these size issues are exacerbated in developmental studies, both prenatal and neonatal. As miniaturization of techniques, assays, and equipment occur, careful attention needs to be paid to the increase in skill and particularities needed, as otherwise reproducibility of data may suffer. Technical challenges will need to be met in order to obtain conscious measurements of cardiac output and regional blood flow, to carry out CNS recordings and infusion, and to miniaturize all of the many biochemical assays. However, many of these are not insurmountable and, by working together, the rodent model users can find ways to accomplish these goals.

The field of cardiovascular physiology has seen a major animal model change in the 1970s, when it became increasingly difficult to use the mongrel dog. The transition from the dog to the rat as the predominant research model in cardiovascular research occurred slowly over about a 15 year period as retooling related to size and scaling factors occurred and young investigators were trained in requisite new techniques. Although there are relatively fewer investigators doing systems physiology now, as compared to the 1970s and 1980s, with an appropriate investment of time and resources, a solid understanding of mouse physiology and biochemistry could, and should, be obtained. However, as stated previously, the rat model most closely mimics the human condition for many health and diseases areas, because of a different basic biology that cannot be recapitulated by ENU-mutagenesis in the mouse. Therefore, investment in the genomic and

genetic tools for rat will be a sound and cost-effective approach for understanding pathobiology and developing new diagnostic, prevention, and treatment approaches for human health and disease.

III. ACCOMPLISHMENTS, NEEDS, AND OPPORTUNITIES

The workshop participants identified two general area of opportunities and needs. These two areas are biology/physiology and genomic infrastructure. Biology/physiology needs and opportunities consisted of germ-line modification, a National Rat Genetic Resource Center, a Rat Genome Database, mutagenesis and phenotyping, and strengthening the rat model user research community. Genomic infrastructure needs and opportunities consisted of an expanded EST program, SNP development and mapping, enhanced BAC libraries, and pilot DNA sequencing. Each opportunity and need is described below.

A. BIOLOGY/PHYSIOLOGY

1. Germ-line Modification

The need for access to the germ-line of the rat in order to produce informative mutants is critical. The availability of gain of function (over-expression; knock-in) and loss of function (knock-out) mutations in the rat will be necessary for the functional characterization of genes. Correct assignment of quantitative trait loci (QTL) to genes will require verification from loss of function mutations or gene replacement studies. Although the production of transgenic rats is now routine, the creation of loss of function mutations by homologous recombination in embryonic stem (ES) cells has not yet been possible in the rat. The production of ES like cells for the rat has been accomplished in a number of labs using both standard methodology or selective ablation of differentiated cells with Oct4 promoters in transgenic blastocysts. Although these cells are morphologically like ES cells and carry a variety of markers that indicate they have not committed to differentiation pathways and hence are likely to be pluripotent, they have so far failed to produce germ-line chimeras useful for generation of targeted mutations.

An alternative approach for routine production of loss of function mutations in a variety of strains and transgenics is nuclear transfer (NT), in which a nucleus from cultured cells with targeted mutations is placed in the enucleated egg of the animal and then developed to term. The nucleus so transferred carries the mutation desired and, for all practical purposes, defines the strain of the offspring obtained. Animals produced by nuclear transfer of embryonic or adult cells have been obtained from primates, pigs, rabbits, mouse, cows, and sheep. Offspring produced from zygotic fusion have been obtained in the rat. Animals produced by nuclear transfer with genetically modified cells have been obtained for cows and sheep, suggesting the general strengths of the overall strategy.

Nuclear transfer consists of several steps, including egg obtainment, enucleation of the egg, fusion of the donor cell or insertion of the donor nucleus, activation of the egg and transfer to a surrogate mother for development to term. In the rat, many labs have achieved the efficient

collection of eggs by superovulation with hormones, laying the ground-work for pursing studies in this area. Both fusion and injection of nuclei lead to preimplantation development in the rat. Development of live offspring following transfer of embryos to surrogate mothers is routine in the rat. The birth of an offspring from this process would provide a heterozygous mutant animal if the donor nucleus had come from a cell with a heterozygous targeted mutation.

The efficiency of embryo transfer with respect to development of live births is greatly influenced by time spent in suboptimal culture. Moreover, the assessment of developmental potential of the eggs following NT is best done using in vitro culture allowing direct visualization of the preimplantation stages of development. However, there are very few systems that allow robust development from one cell fertile eggs to the blastocyst stage of the rat embryo. One such system, R1ECM, works well for Wistar outbred and Sprague Dawley outbred rats, but not for other, particularly inbred, strains. Progress with NT would be accelerated if a culture system that worked well with many inbred as well as outbred strains were available.

2. National Rat Genetic Resource Center

In August 1998, NIH convened a meeting entitled NIH Rat Model Repository Workshop (http://www.nhlbi.nih.gov/nhlbi/sciinf/model/ratmodel.htm). The recommendation of the workshop was, in order to meet the needs of the broad rat research community and to provide the foundation for consistent and well-characterized rat models for human disease, to establish a national, central repository resourceCa National Rat Genetic Resource Center (NRGRC). The main functions of the NRGRC would be as follows:
(1) maintain and characterize the most widely used rat strains; (2) preserve valuable strains, including transgenic strains, through cryopreservation; (3) distribute genetically and microbiologically high-quality animals;
(4) provide information, advice, and training in the use of genetically defined rat strains; (5) contribute to the research and development of technological advances in cryopreservation, embryo culture, and animal maintenance;
(6) 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 participants of this current meeting unanimously agreed that the NRGRC is central to effective rat model research and endorsed the recommendations of the previous report. With the rich biological and behavior history of the rat model and the upcoming genomic tools and genetic applications, a repository for the large number of current, and future, inbred, transgenic, and congenic strains is a high priority.

3. Rat Genome Database

In response to the recommendations of the Rat Genome Advisory Committee and the Report of the NIH Model Organism Database Workshop (http://www.nhlbi.nih.gov/), the NIH has issued a request for applications (RFA) for a Rat Genome Database (RGD). The

objective of this RFA is to establish a database that will collect, consolidate, and integrate data generated from ongoing rat genetic, genomic, and related research efforts, and to make these data widely available to the scientific community. The applications were due on April 30, 1999 and an award is expected September 30, 1999. The participants strongly endorsed this plan for NIH to implement an RGD. Rat genomic, genetic, and phenotypic data needs to be easily and readily accessible to all researchers. The participants also requested that the Rat Community Forum web site continue, although support for the web site was not discussed. Since the meeting participants considered the implementation of the RGD to be underway, it was not considered in the final priority list. However, the RGD was seen as absolutely essential.

4. Interaction with the NIH Mouse Mutagenesis and Phenotyping Program

Mutagenesis and phenotyping of rat models, in parallel with the NIH mouse mutagenesis and phenotyping program, will allow significant interaction and collaboration on developing new rodent models of human disease, with comparable characterization. Random mutagenesis can offer the rat model an alternative to gene targeting strategies, as many of the induced mutations are loss of function. In addition, if rat and mouse mutagenesis and phenotyping programs are established together, each can benefit from the others experience. There is significant intellectual capital in the rat physiology and behavior communities. This knowledge-base should be involved in the translation of the physiological and behavioral methods needed by the mouse phenotyping program and to establish comparative studies of these procedures in the mouse and rat models.

5. Strengthening the Rat Model User Research Community

A major success of the meeting was catalyzing the formation of an interactive research community of rat-users. A web site (Rat Community Forum) was established in advance of the meeting to pose a series of 8 questions to this community at large. The community was identified via email lists from several societies affiliated with FASEB. The member names were screened against Medline and rat-users identified. The rat-users were then sent a single message to visit a web site to comment on the 8 questions posed for the meeting. In total more than 130 rat-users from a diverse range of fields responded to the questions. These responses, in conjunction with the diversity of research topics represented by the meeting participants, provided a unique opportunity to exchange ideas about building unity, capitalizing on opportunities, and exchanging ideas within this community. Dr. Varmus suggested the community develop a rat contact group to interface with the NIH. Several suggestions were made to further develop the community:

a. The Rat Community Forum (RCF) web site (http://goliath.ifrc.mwc.edu/RCF) should remain open.

b. Participation in a series of rat genetic based meetings scheduled.

    1. Physiological Genomics in the Rat, Cold Spring Harbor Laboratories. December 5–9, 1999.

2. Rat Genetics and Genomics Meeting, Goteborg, Sweden. June 13-16, 2000.

3. Rat Genetic and Genomics Meeting, Milwaukee, WI. Summer, 2001.

c. Satellite rat genetics meeting in conjunction with The 13th International Mammalian (Mouse) Genetics Conference, October 31–November 3, 1999 in Philadelphia, PA., as well as future International Mammalian Genome Society activities.

d. Satellite rat genetics and phenotyping meeting in conjunction with the American Society of Human Genetics.

Many of these meetings and interactions are already being planned. The participants were very enthusiastic about continued interaction, with NIH providing support through staff involvement (identify speakers and topics, develop agendas, etc.) and funds for conference grants and meetings.

B. GENOMIC INFRASTRUCTURE

Recognizing the usefulness of the rat as a model system, NIH funded the Rat Genome Project (RGP) and the Rat Expressed Sequence Tag (REST) Project to develop important genomic tools and resources that will further enhance the power of rat model systems (Table 1). These two infrastructure projects, and the RFA for the Rat Genome Database, provide the ability to link the rat physiology and functional biology with the genetic tools of the mouse and the clinical features of the human through comparative mapping to facilitate the translation of bench to bedside. However, much is left to be done to fully and effectively capitalize on the opportunities the rat provides.

Table 1: Existing Rat Genomic Tools

Tool	Site(s) Where Developed
Genetic Markers and genetic maps	Whitehead/MIT, MGH, MCW, University of Iowa, NIH, Oxford and Otsuka Pharmaceutical Company
YAC libraries	Whitehead/MIT, German Rat Genome Project
PAC library	Roswell Park Cancer Institute
BAC library	Roswell Park Cancer Institute
Radiation Hybrid Panel	Cambridge/Research Genetics
Radiation Hybrid Map	MCW, University of Iowa, Oxford and Otsuka Pharmaceutical Company
Normalized cDNA libraries	University of Iowa
I.M.A.G.E clones	U of Iowa, Research Genetics
Rat ESTs	U of Iowa, TIGR
Rat UniGene Clusters	NCBI
Dense Mapping Cross	German Genome Project, MCW

1. Rat EST (REST) Project

The REST project has generated more than 93,000 ESTs derived from 12 different normalized cDNA libraries. These normalized libraries combined with a serial subtraction strategy have provided an unprecedented level of efficiency with respect to identifying unique rat genes, a set of 27,000 UniGene clusters. This is a marked improvement over the 15,000 mouse UniGene clusters generated from more than 300,000 ESTs. The REST also has the goal of mapping 8,000 ESTs on the radiation hybrid map. Additionally,

1,500 ESTs with sequence homology to human ESTs or genes have also been placed on the RH map, thereby facilitating the development of more accurate comparative maps. The NIH has approved a competitive renewal of the REST. If the applications are approved, they would increase the number of UniGene clusters in the rat to 60,000, with 27,000 of these ESTs mapped onto the radiation hybrid (RH) map. The participants were very enthusiastic about the progress of this project, and recommended the goal be expanded to achieve 90% coverage of all rat genes. It was recognized that this goal would require careful monitoring to insure that novel genes were continuing to be discovered at reasonable cost.

2. SNP Discovery and Mapping

The rat genetic map and the rat radiation hybrid map have more than 8,000 genetic markers (primarily microsatellites). These maps enable investigators to identify chromosomal regions (QTLs) that

contain genes responsible for specific phenotypes. It is evident from both this meeting and the literature that a large number of investigators are using rats to successfully locate QTLs that are models for common human disease. However, the density of markers currently available is nearly an order of magnitude short of the number of markers that will be required to positionally clone genes from the mapped positions. To overcome this limitation, the participants suggested constructing a 3rd generation genetic map using single nucleotide polymorphisms (SNPs) at a resolution of 1 SNP per 100 kb.

3. BAC Clone Resources

One of the major goals of the RGP is to build the initial physical mapping tools in the form of a series of large insert libraries for genomic DNA. The International Rat Genome effort has generated two 10-fold rat YAC libraries, a >10-fold PAC library, and a >10 fold BAC library. These physical mapping reagents are useful for initiating individual positional cloning projects and are being used by many laboratories around the world. However, with the change in sequencing capacity in both the public and the private sector it is important to consider if these reagents position the rat for the sequencing of its full genome, once the mouse genome is sequenced. Several of the participants have evaluated the BAC resources and determined that the size of the inserts combined with the use of a single restriction enzyme limit the use of existing BAC resources for sequencing. Therefore, there is a need to develop a BAC library with 15-fold coverage made from multiple sources of DNA cut using a variety of restriction enzymes or random shear techniques while still maintaining an average insert size greater than 150 kilobases.

4. Genomic Sequence

Within less than two years the sequencing capacity of the publicly funded US and International Genomics community is likely to pass that needed to sequence a mammalian genome to 10-fold redundancy in one year. The rat should be positioned for genomic sequencing immediately after, or in parallel, with the mouse. Support for near term finished sequencing of 5-10 megabases of the rat genome in at least 1 megabase parcels should be a goal. Syntenic regions corresponding to mouse and human genomic intervals slated for immediate sequencing should be prioritized. Detailed analysis of this sequence, community response, as well as simulations based on this data set, will provide an empiric basis for selecting an appropriate genomic sequencing strategy for the rat.

II. RECOMMENDATIONS AND PRIORITIES

The needs and opportunities for the rat model identified and described above were prioritized at the meeting by the participants. Although the initial discussions grouped the recommendations into two groups (biology/physiology and genomic infrastructure), the prioritizing discussions pulled out the most critical initiatives based on need and opportunity.

The final recommendations are listed in priority order.

1. **Germ-line Modifications**
($8.5 million over 5 years)

(See Accomplishments, Needs, and Opportunities; Biology/Physiology; Germ-line Modifications: section III/A/1)

Germ-line modification in the rat is critically important to assigning gene function to specific genes and to identifying gene alterations responsible for specific phenotypes. The analysis of phenotypes from gain of function and loss of function has been the most direct and useful way to connect specific genes to phenotypes relevant to human disease. Although the production of transgenic rats is routine, the accessibility to this technology is limited and needs to be extended. Transportation and storage of valuable transgenics is problematic. The development of ES like cells in the rat is routine, but these fail to make germ-line chimeras and therefore cannot be used to take advantage of homologous recombination for knock-outs and knock-ins. The highest priority should be to overcome these limitations, thorough the use of the following strategies: (a) The development of nuclear transfer in the rat is an important priority that needs to be met ($5 million over 5 years). (b) The development of dominant negative mutations by pronuclear injection should be encouraged ($500,000 per year for 5 years). (c) Cryopreservation of zygotes and sperm will help to alleviate the storage and transportation problems ($750,000 over 5 years). (d) The generation of in vitro fertilization (IVF) techniques in the rat, including intracytoplasmic sperm injection (ICSI), will help the use of cryopreserved sperm by allowing suboptimal sperm to lead to viable offspring ($250,000 over 2 years). ICSI has been achieved in the rat and its use could be easily optimized and made generally available. The developments from this research could be transferred to the NRGRC for implementation in that resource and for distribution to the research community.

2. Additional Genomic Resources
($30 million over 3 years)

(See Accomplishments, Needs, and Opportunities; Genomic Infrastructure: section III/B/1,2, 3,4)

a. EST Project Enhancement ($2.5 million per year for 3 years): The participants were very enthusiastic about the progress of this project, and recommended that the goal be expanded to achieve 90% coverage of all rat genes. Achieving this goal will offer significant advantages and opportunities. It will identify rare transcripts in specific tissues of interest, as well as in specific developmental stages. It will also allow the development of a finer syntenic map with the mouse and human, which will greatly improve efforts in identifying genes and elucidating their function.

b. SNP Discovery and Mapping ($6.5 million over 3 years): Developing a SNP map of the rat is a high priority, as it is required to accelerate the identification of genes (through positional cloning) responsible for complex, common diseases. There are multiple strategies for developing SNPs. While no formal requirement was stated as to how SNPs should be

developed, the participants recommended that the existing rat EST project be used to leverage NIH resources. As outlined previously, one of the goals of the competitive renewal of REST (assuming funding) is to develop a rat UniGene set consisting of 60,000 ESTs. Of these 60,000 ESTs, 27,000 will be mapped on the RH map and therefore provide ideal starting points for the SNP map, as the primers that have been developed for the mapping can be used for SNP selection. The other 33,000 ESTs also provide a rich source of sequence data for initiating the development of SNPs, assuming this project is renewed (competitive) this year.

c. *BAC Clone Resources ($1 million for 1 year)*: Sequencing the rat genome should be placed at very high priority as the third mammalian genome to be sequenced after man and mouse. However, the necessary clone resources must be developed quickly. The capacity of the publicly funded genome sequencing efforts will most likely exceed 20 raw megabases per year by the spring of 2000. It therefore seems likely that aggressive sequencing of the rat could commence before 2004, with a high quality draft being possible a year thereafter. The key prerequisite for such an effort is a high quality well characterized, and deeply redundant BAC library. This library should have large inserts (average size greater than 150 kilobases), be redundant to a depth of 15-fold or greater, and ideally be produced by more than one restriction enzyme or physical shearing. The currently available BAC library is unsatisfactory with respect to insert size, and is the product of a single restriction enzyme.

   Additionally, at least a 10-fold subset of these BAC clones should be subjected to end sequencing and restriction fingerprinting. This is an essential resource to permit efficient genomic sequencing with a minimum investment in mapping.

d. *Pilot Sequencing ($15 million over 3 years)*: A complete sequence of the rat genome will provide the critical substrate for understanding the molecular basis of biological function and pathology. A coordinated and systematic approach will be most cost effective. It is however not yet clear how to optimally sequence the rat given the existence of the sequence for mouse and man, a rich array UniGene models from all three species, and the need to address further genomes. It may be that some form of 'draft' sequence in the rat would strike the best cost/benefit balance. To address this question, a small number of rat genome sequencing pilot studies, each covering a few megabases, should be performed. Regions homologous to ones already sequenced in both man and mouse should be selected. The already available rat BAC library should be used for the source of clones.

3. National Rat Genetic Resource Center ($35 million over 5 years)

(See Accomplishments, Needs, and Opportunities; Biology/Physiology; National Rat Genetic Resource Center: section III/A/2)

The genetic integrity of, and access to, important rat strains is maintained by an international effort that depends on the personal good will of many individuals. This effort is inherently inefficient and susceptible to the vicissitudes of funding and local interests. A much more robust approach to the problem of genetic integrity, microbiological quality and distribution of these valuable models would be the National Rat Genetic Resource Center (NRGRC).
The objectives of the NRGRC are 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; 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 disseminate information concerning germ-line modification techniques to the scientific community; to provide relevant information to the scientific community via a Web page that interfaces with other rat databases; and to sponsor meetings to discuss various uses of the rat in biomedical research and the developments in rat genetics and genomics.

Establishment of the NRGRC will have a broad impact on a wide range of research areas by providing an effective source of quality, transportable animals and embryos that will meet the current needs and anticipated increased demand due to the development of important genomic tools and resources in the rat. Lack of accessibility to strains of known microbiological and genetic quality is a major limitation to studies using inbred rat models, as commercial suppliers carry a very small subset of inbred rat strains and genetic purity data are not always available.

If necessary, a smaller pilot of the NRGRC could be envisioned to establish utility. The participants noted that the cost of the NRGRC could be reduced by adopting user fees and encouraged NIH to consider creative solutions to the long-term support of the repository, including a potential commercial supplier to fill this critical niche.

4. Interaction with the NIH Mouse Mutagenesis and Phenotyping Program ($1 million per mouse center)

(See Accomplishments, Needs, and Opportunities; Biology/Physiology; Interaction with the Mouse Mutagenesis and Phenotyping Program: section III/A/4)

Mutagenesis and phenotyping of rat models should be incorporated into the NIH Mouse Mutagenesis and Phenotyping RFA program. Direct interactions between the rat physiologists and the mouse geneticists will enhance the utility of discovering and characterizing new models for human disease. Direct participation will also increase the likelihood of technology and know-how transfer between the rat and

mouse research communities. In this way, the mouse research community can gain expertise and knowledge in phenotypic methods, while the rat research community will gain expertise and knowledge in genetic manipulation. The involvement of the rat physiologists and behaviorists in translating established norms and protocols used in the rat to be applied in the mouse will be of great benefit to both rat and mouse user communities.

This direct collaboration and translation will allow empirical data to be gathered using side by side comparisons of each model in various physiological, biochemical, behavioral, and surgical measures and procedures. In addition, genome-wide, random mutagenesis offers an alternative approach to gene targeting strategies.

V. SUMMARY

Rat models offer exciting opportunities to understand human health and disease. Their use to understand complex diseases and biological phenomena requires the highest quality and most effective genomic and genetic tools and resources and a functional infrastructure. Such comprehensive resources, as delineated in this report, are needed for effective identification of genes responsible for disease and health, defining gene function, understanding how genes interact with the environment and with each other, discovering and testing new drugs, and designing new prevention strategies.

NIH Rat Model Priority Meeting

Lawton Chiles International Center
Bethesda, MD
May 3, 1999

Agenda

Plenary Session

7:15 a.m.	**Registration and Continental Breakfast**	
8:00 a.m.	**Introduction**	Dr. Varmus
8:20 a.m.	Overview	Dr. Branscomb Dr. Cowley
8:30 a.m.	Rat Genome Tools, Resources, and Applications	Dr. Jacob
8:55 a.m.	Cardiovascular Physiology	Dr. Cowley
9:20 a.m.	Behavioral and Neuropharmacology of Addiction	Dr. Samson
9:45 a.m.	*Break*	
10:10 a.m.	Arthritis and Related Autoimmune Disorders	Dr. Wilder
10:35 a.m.	**Learning, Memory, and Behavior**	Dr. Eichenbaum
11:00 a.m.	Reproductive Physiology and Endocrinology	Dr. Conn
11:25 a.m.	**Rat Models Using Transgenesis**	Dr. Mullins
11:45 a.m.	Embryonic Stem Cells and Nuclear Transfer Technologies in the Rat	Dr. Iannaccone
12:05 p.m.	Follow Up Discussions	Dr. Branscomb Dr. Cowley
12:30 p.m.	*Lunch*	

Open Discussion
Key Questions and Responses from
The Rat Community Forum: http://goliath.ifrc.mcw.edu/RCF/

1:30 p.m. **Issue A: Comparative Value** **Dr. LaVail**

Question 2: What are the strengths and weaknesses of rat models of health and disease, and how do they compare to the strengths and weaknesses of mouse models (for example, what can be done in the rat that can't be done in the mouse; what can be done in the mouse that can't be done in the rat)?

Question 3: Are the rat and mouse sufficiently close evolutionary and physiologically to each other that continued investment should be restricted to one mammalian model system?

Question 5: Does the rat occupy a unique and essential place in studying health and disease that cannot be served by technological (e.g. miniaturization of assay systems) advances in the mouse?

2:00 p.m. **Issue B: Functional Genomics** Dr. Walker

Question 1: What is the likely impact of these genomic resources and reagents for the rat on defining gene function and increasing our understanding of common diseases that afflict humans?

2:30 p.m. **Issue C: Infrastructure** **Dr. Blankenhorn**

Question 4: How would further development of genetic and genomic infrastructure for the rat (e.g., ES cells, nuclear transfer, Jackson Lab-like repository for the rat, synteny map(human/mouse/rat), genomic sequence, database) enhance the utility of the Human Genome Project and our ability to understand common human diseases? What will be lost if the rat infrastructure does not keep pace with other model organisms and the Human Genome Project?

Question 8: What are the consequences of not developing the infrastructure of the rat any further?

3:00 p.m. ***Break***

3:30 p.m. **Issue D: Physical Resources** Dr. Duyk

Question 6: Within less than two years the sequencing capacity of the publicly funded US and International Genomics Community is likely to pass that needed to sequence a mammal to 10X redundancy in one year. The second major target for this capacity will certainly be the mouse. What impact should these expectations have on how genomic infrastructure should be developed for the rat. What is the optimal targeting approach for sequencing in the rat given such capacities and the existence of full genomic sequence from mouse and human? What resources should be made available, and when to allow rat genomic sequencing to be most effectively undertaken?

Question 7: Are there benefits of having mouse, human, and rat genomic sequence available?

4:00 p.m. **Needs, Opportunities, and Future Directions** Dr. Branscomb
Dr. Cowley

5:00 p.m. *Adjourn*

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