The Jackson Laboratory
Leading the search for tomorrow's cures

December 3, 2010

Mr. Norman Augustine, Chair
Scientific Management Review Board
NIH Building 1, Room 103
9000 Rockville Pike
Bethesda, MD 20892
smrb@mail.nih.gov

Dear Mr. Augustine and Members of the Scientific Management Review Board:

The Translational Medicine and Therapeutics Working group of 11/10/10 discusses progress in planning to speed the translation of basic research discovery to clinical practice. On behalf of The Jackson Laboratory, we applaud the goal. As a national research, education, and resource center for the biomedical research community, our faculty and staff are committed to participating in the transformation of medicine that will result from applying recent discoveries to the clinic. It is in our role as a nationally recognized resource center that we write to request that great care and thought go into how the divisions of NCRR that support basic discovery are handled in this reorganization to stimulate translational research.

In particular, we request that you consider including the Division of Comparative Medicine in the proposed new IC. The proposed goals to provide and support resources, training and tools to enable translational and therapeutics development research are a strong fit with the Division's mission to provide model organisms and information to researchers. This will be particularly important in the new IC's efforts to "amplify the connection between basic discovery and translation." Given the importance of model organisms in the pipeline for producing individualized therapeutics, it will be critical to coordinate the Division's model organism resources with the new IC's work to streamline the therapeutic development pipeline.

Two projects funded through revision awards to grants that support our mouse repositories (P40RR016049 and P40RR001183) exemplify the benefits of coordinating the CTSA program with the Division of Comparative Medicine. These collaborations leverage the strengths at each institution to speed the application of basic discovery to preclinical and clinical testing.

- **Investigating the biological consequences of aneuploidy in early embryogenesis,** a collaboration with University of Michigan Transgenic Animal Model Core Facility (UMTAMCF, a university ABMR), and several research groups affiliated with the Michigan Institute of Clinical Health and Research (MICHR, CTSA awardee) in a combined effort to (1) enhance our understanding of the early embryonic consequences of aneuploidy using several genetic mouse models and (2) develop new resources for studying aneuploidy.
- **Development of the bENaC model of cystic fibrosis for translational research**, a collaboration with the Cystic Fibrosis Research and Treatment Center at The University of North Carolina at Chapel Hill. The project aims to identify novel genetic modifiers of the *Scnn1b* mouse model for cystic fibrosis and develop the model for preclinical testing protocols. This work supports the translational research goals of the North Carolina Translational and Clinical Science (TraCS) Institute (an NCRR-supported CTSA).

Grants from NCRR support research and resources at many U.S. institutions. As an international resource center, we at Jackson can clearly see the breadth of research enabled by NCRR support. Long-term funding from NCRR for Jackson's resource mission is fundamental to our ability to serve the biomedical research community. Jackson has long been the primary resource for genetically defined mice for the national research endeavor, and a glance at our distribution history and statistics reveals the enduring and widespread utility of these NCRR-supported research reagents.

Our scientists have developed and distributed inbred and mutant strains of mice since the institution's inception. NCRR (formerly the Division of Research Resources) has funded the characterization and distribution of spontaneous mutations arising in our distribution colonies continuously since 1978. Thousands of mice representing spontaneous mutations resulting in disease phenotypes have been distributed from our NCRR funded repository. Along with the Mouse Mutant Resource, JAX and the NCRR established the Special Mouse Strains Resource (SMSR) for recombinant inbred (RI) and consomic strain (CS) panels in 2001. This resource has the largest collection of RI and CS sets in a single repository and distributes them to labs world-wide.

In 1992, at the request of the scientific community, Jackson developed the first national repository for transgenic and targeted mutant mice, ensuring the preservation, genetic and health quality, and distribution of the rapidly expanding numbers of mouse models for human diseases. This Induced Mutant Resources was at first funded through private foundations, and since 1993 by grants from NCRR. Of the over 2000 mutant strains the Induced Mutant Resource has imported and developed, most have been cryopreserved, nearly half are maintained in breeding colonies, and many hundreds of thousands of mice have been distributed to biomedical researchers world-wide. Our experience with the Induced Mutant Resource paved the way for the NCRR-funded Mutant Mouse Regional Resource Centers (MMRRC) and other international resources, with whom we collaborate. The Division of Comparative Medicine is an influential leader in efforts to make these valuable research reagents available rapidly and cost-effectively.

It would not have been possible for us to manage this ever-increasing number of strains without continuous funding since 1981 from the Division for our cryopreservation research and resources. Advances in the ability to reliably recover embryos from diverse inbred and mutant strains of mice enabled us to preserve mice in low demand. Recognizing the crucial role of cryopreservation in managing the exponentially increasing number of new animal models, the Division of Comparative Medicine co-organized a workshop at NIH in April 2007 entitled "Achieving High-Throughput Repositories for Biomedical Germplasm Preservation." The results of this workshop guided the funding priorities that have supported breakthroughs in cryopreservation here and elsewhere that now make possible efficient management of large numbers of small colonies of specialty mice.

Our specialty colonies have now been combined into *The Genetic Resource Science (GRS) Repository,* which maintains more small colonies of live mice than all other U.S. public repositories combined (determined from queries of public web sites). Although a number of disease-specific agencies fund small colonies within the Repository, the majority of the funding for new strain acquisitions is supported by NCRR. Maintenance and distribution of mice are self-supporting. Typically, the GRS Repository has approximately 1,500 live strains on the shelf available for distribution at any one time. The size of individual colonies is constantly monitored and adjusted according to demand within a fixed capacity. Requests for breeder pairs and small cohorts of mice are fulfilled, with larger experimental groups available by special arrangement. The thousands of Repository mice distributed reflect both the value of this resource to the community and the efficiency of distribution operations. The number of live mice distributed from the Repository annually has steadily grown from about 40,000 in FY2006, to 85,853 in FY2010. The average processing time from request to shipping has remained at 2-4 weeks in spite of this increased demand.

Today, three fourths of the 5,000 mouse strains distributed by Jackson are managed exclusively as cryopreserved embryos, sperm, or ovaries, saving $14 million per year in operating costs while ensuring the availability of these vital resources in perpetuity. During the most recent 6 months, the Reproductive Sciences group:

- Filled 583 orders for cryopreserved materials including ES cells, mouse embryonic fibroblasts, tissue, sperm, and embryos;
- Recovered 1,200 strains from cryopreserved embryos or sperm for orders or as part of QC processes;
- Produced 18,000 mice to fill 917 orders from 27 countries for strains that had been cryopreserved.

This scope of resource provision would not have been possible without support from NCRR.

In addition to the major support of mouse resources, funding from other NCRR divisions is essential for our ongoing research and training endeavors that underlie our ability to characterize the genomes and phenotypes of the research resources we distribute. Eleven shared instrumentation grants from the Division of Biomedical Technology have purchased equipment including a range of advanced microscopes, flow cytometry and blood chemistry analyzers, first and second generation DNA sequencers, and a spectral karyotyping system. These instruments have been used to characterize models of a variety of human diseases including neurosensory loss, infertility, cancers, sickle cell anemia, metabolic diseases, neurological disorders, kidney disease, and immune disorders, among others. Fourteen grants from the Division of Research Infrastructure have supported improvements to our research animal facilities that house the Repository colonies, our quarantine facility, and laboratories for phenotypic characterization of mouse models. The Division of Research Infrastructure also supports the IDeA program, including the INBRE program, in which Jackson participates to offer students from Maine institutions access to our internship and workshop programs. We strongly urge you to maintain the full function of these vital national resource providers in any reorganization plan you undertake.

Thank you very much for your consideration of our request. NCRR's role in providing resources for basic and translational researchers is crucial to the success of efforts at NIH to advance therapeutic development. In particular, the role of the Division of Comparative Medicine in developing appropriate resources and stimulating interactions among basic and translational scientists merits its inclusion in a new IC for translational medicine.

Sincerely,

Robert Braun, PhD, Associate Director/Chair of Research

Leah Rae Donahue, PhD, Director Genetic Resource Science

Valerie Scott, Senior Director, Scientific Services

David Valle, MD, Chair, Board of Scientific Overseers
Henry J. Knott Professor and Director, Institute of Genetic Medicine, Johns Hopkins University School of Medicine

David Burke, PhD, Chair, Genetic Resource Science Advisory Board
Professor of Human Genetics, University of Michigan Medical School

cc: Dr. Francis Collins
Dr. Lawrence Tabak