SUMMARY

Second Follow-Up Workshop on Priority Setting for Mouse Genomics and Genetics Resources

May 26, 2000

Bethesda Marriott Hotel, Bethesda, Maryland

BACKGROUND

The purpose of this workshop was to inform the scientific community of NIH's progress in responding to the recommendations of the Priority Setting for Mouse Genomics and Genetics Resources Workshop held in February 1998. It was also an opportunity to determine which recommendations were still appropriate and what new resources were needed. Approximately 30 mouse biologists, geneticists and investigators involved in high throughput genome sequence generation were invited to discuss these issues in an interactive environment. The invitees were briefed by NIH staff on progress that had been made in response to previous recommendations. International invitees provided an oversight of programs outside the United States and three invited presentations were given--one on the cloning of mice by nuclear transfer, one on database design for phenotypic data, and one on the mouse phenome project.

A. FUNCTIONAL GENOMICS

Progress

- The NIH currently supports 12 extramural and intramural mutagenesis and phenotyping projects focused on a broad range of phenotypic alterations (e.g., defects in sleep, neurologic function, development, and complex behavior). A Request for Applications (RFAs) was issued in 1999 to solicit facilities to conduct large-scale mouse mutagenesis and phenotyping of nervous system function and complex behavior. Two large collaborative projects will be funded, with a total investment of $28 million over 5 years. Soon to be under review are applications received in response to a second RFA that aims to establish mutagenesis and phenotyping facilities focused on developmental defects; these facilities are expected to be funded by Fall 2000. These Centers will screen for both dominant and recessive mutations. A central database will provide a detailed description of the mutant phenotypes developed. Through a Determination of Exceptional Circumstances under the provisions of the Bayh-Dole Act, all animals under both initiatives will be freely available to the community.

- Complementary mutagenesis and phenotyping projects are also being undertaken in Germany, United Kingdom, France, Canada, Japan, and Australia.

- The NIH supports 35 mouse projects to develop improved, high-throughput phenotyping assays in the areas of nervous system, behavior, immunology, sleep, eye, and bone. Additional initiatives under development are focused on mouse screens for heart, lung and blood diseases, diabetes, metabolic disorders, drug abuse, and miniaturized assays to measure hormones, ions and metabolites in small tissue volumes.

- Success in cloning mice using donor nuclei from adult somatic cells and ES cells was reported. While efficiencies are low, there are many factors in need of systematic exploration.

- The Jackson Laboratory is in the process of establishing baseline phenotypic data on commonly used and genetically diverse inbred mouse strains. The information on these animals will be available through a publicly accessible database.

Recommendations

1. Databases of phenotypes will become the common currency in research. Phenotyping data are more complex than genome sequence data and therefore, much thought and creativity should go into the development of such databases. Because of this complexity, it may be desirable to support pilot projects to develop prototypes initially, but these must be interoperable**.**

2. Develop improved technologies for targeted mutagenesis, especially in cell culture.

3. Develop technology to clone mice using somatic nuclear transfer with greater efficiency.

4. Continue to develop more robust and sophisticated phenotyping assays. Encourage the application of experience from other fields such as nanotechnology and bioengineering.

5. On an international basis, make animals produced by mutagenesis studies widely available to researchers unencumbered by complex material transfer agreements.

6. Hold periodic meetings of representatives from international centers conducting mutagenesis and phenotyping to avoid duplication and facilitate the exchange of phenotypes.

7. Encourage collaborations with industrial partners in order to capitalize upon technology that can facilitate genetics and genomics research.

B. STRUCTURAL GENOMICS

Progress

- NIH has funded ten centers to produce mouse genomic sequence and to develop resources for genomic sequencing, such as a databases of BAC fingerprints and paired-end sequences from BAC clones. NIH anticipates that a 2X-3X coverage of the mouse genome will be available in the next year and complete sequence by 2005. Three of the funded centers are engaged in a program to sequence BACs of high biomedical importance. A private effort is underway to sequence three different mouse strains at 1X coverage.

- The international genome sequencing efforts include: (i) An effort in the United Kingdom will sequence 50 Megabases of DNA from mouse chromosomes 2, 4, 13 and X by 2002. It also has two mapping centers and a small program to sequence BACs of biomedical importance. (ii) Germany plans to sequence 2.9 Megabases of DNA from mouse chromosomes 1, 4, 11, 19 and X that are homologous to human chromosome 8. (iii) France plans to do some mouse sequencing, but no decision has been made about which regions. (iv) Japan does not currently have plans to sequence the mouse genome. The international efforts will focus on finished rather than draft sequence.

- NIH supports the Mammalian Gene Collection, which is a collection of full-length cDNAs from human and other mammalian genes. The goal is to capture "transcript diversity." With respect to the mouse gene collection, cDNA libraries will be made from 15 different tissues and it is anticipated that 20,000 near full-length human or mouse cDNAs will be sequenced per year. The sequences will be deposited in a public database and the clones will be made freely available to the community. An effort is underway to map 20,000 mouse ESTs.

Recommendations

1. Complete the genomic sequence of the C57BL/6 mouse to the same level of completion as the human genome.

2. Generate BAC libraries from additional mouse strains: 10X coverage for two or three strains and 2X-3X coverage for six to eight strains.

3. Assemble a unigene set of mouse cDNAs that is readily available, comprehensive and ready for array technology. Full-length cDNAs are not necessary for this resource.

4. Accelerate positional cloning in the mouse by improving genotyping technology, by developing new techniques to increase recombination frequency or to induce a high frequency of cross-overs useful for high resolution mapping, and by developing non-meiotic techniques

C. RESOURCES AND TRAINING

Progress

- The NIH has developed several types of training programs to increase the number of mouse pathobiologists. The types of awards include three career development awards: Special Emphasis Research Career Award in Pathology and Comparative Medicine; Clinical Associate Physician Award; and Mid-Career Investigator Award in Mouse Pathobiology Research. In addition, the Institutional National Research Service Award provides support for pre- and post doctoral students in the comparative medical sciences.

- Four additional Mutant Mouse Regional Resource Centers have been funded. The overall goals of the Centers are to import, re-derive and produce high-quality genetically-engineered mice (GEM), cryopreserve and store GEM germplasm; distribute locally, regionally and nationally, GEM either as live mice or as cryopreserved germplasm; perform genotyping, phenotyping and infectious disease surveillance of GEM strains; and conduct innovative research. A data coordinating center has been funded to develop and maintain data on all strains maintained at the Centers; to develop and implement an information network linking the Centers; to develop and maintain a Web page to facilitate on-line ordering; and to establish procedures for coordinating investigator support services and distribution.

- Five grants have been funded to improve cryopreservation.

Recommendations

1. Encourage the training of clinicians and engineers in mouse biology and support multidisciplinary graduate and post-doctoral training that includes mouse biology.

2. Ensure an adequate number of courses in cryopreservation and *in vitro* fertilization are available to meet the demand.

3. Increase the number and size of mouse repositories to accommodate the increased number of mouse strains resulting from the newly funded mutagenesis projects.

4. Encourage and support the use of new high density mouse cages.

It has now been more than two years since the Priority Setting Workshop for Genomic and Genetic Resources in February 1998. Most of the original recommendations have been addressed or overtaken by newer developments. The next meeting on priorities for mouse genomics should take a fresh and comprehensive look at this area.

The recommendations from this meeting will be considered by the trans NIH mouse group. Any program announcements or Requests for Applications related to this workshop will be posted on the Animal Models for Biomedical Research website: http://www.nih.gov/science/models/.

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