National Center for Research Resources
NATIONAL INSTITUTES OF HEALTH

IMPROVING GENETIC RESOURCES FOR THE RHESUS MACAQUE
Bethesda, MD
May 23, 2007

Workshop Summary

The workshop entitled, "Improving genetic resources for the rhesus macaque," sponsored and organized by the Division of Comparative Medicine, National Center for Research Resources, took place on the NIH campus, May 23, 2007. The NCRR thanks the advisory committee for the workshop: Dr. Jeffrey Rogers, Southwest National Primate Research Center (Chair); Dr. Carlos Bustamante, Cornell University; Dr. Stacey Gabriel, Broad Institute of MIT and Harvard; Dr. Richard Gibbs, Baylor College of Medicine; and Dr. Robert Norgren, University of Nebraska Medical Center.

This workshop built on the results of the NCRR workshop of April, 2006, which dealt broadly with the subject of genetic tools for the rhesus (see, Genetic Tools Final Workshop Report) In the interval between the two workshops, a high resolution draft assembly of the rhesus genomic sequence has been published and progress has been made in identifying single nucleotide polymorphisms (SNPs) that will be useful for establishing correlations between specific genotypes and phenotypes in the rhesus. A second workshop in this series was therefore timely, given the significant recent progress in characterizing the rhesus genome.

The purpose of this workshop was to define the next generation of physical and genetic maps that will enhance the use of the rhesus in biomedical research, with an emphasis on a SNP map. A SNP is a variation in sequence at a single nucleotide position in the genome. SNPs occur frequently in primate genomes, are genetically stable and can be assayed relatively easily using high throughput methodologies. Therefore, SNPs have become the markers of choice for developing maps that can be used to understand the genetic contributions to diseases or to other conditions that may vary among individuals.

Topics covered in the workshop were: 1) overview of the use of rhesus in biomedicine; 2) the rhesus genome sequence; 3) status of rhesus SNP discovery; 4) status of sequencing of complex loci of particular biomedical significance such as the major histocompatability complex (MHC); 5) lessons learned from SNP discovery in other species, including humans; 6) high throughput sequencing and genotyping platforms;
7) databases and outreach.

Following these sessions, the participants were asked to define priorities for development of rhesus maps that can be used to obtain correlations between genotypes and phenotypes or to otherwise further the understanding of the correlates of genotype and disease.

Conclusions and recommendations:

- Investigations in progress to sequence the genomes of approximately 20 individual rhesus will help identify many randomly-distributed SNPs that will be useful for development of genotyping assays. These studies should be extended to include at least 300 more animals, with an emphasis on attaining a more complete understanding of

genetic variation among animals from various geographical regions, e.g., animals of Indian *versus* Chinese origin.

- In parallel, characterization of gene-specific SNPs, which currently concentrate on the 3-prime untranslated region of genes of specific biomedical interest, should be continued and expanded. Gene specific SNPs are likely to be of immediate use to investigators.

- In parallel with the SNP discovery efforts, very high resolution sequencing of regions of particular immunological importance should be expanded. Data already exist for the rhesus MHC and the natural killer cell immunoglobulin-like receptor (KIR) locus. The list of complex loci should be expanded and prioritized for high resolution sequencing.

- In addition to sequence differences such as SNPs, variation in gene copy number should be characterized in detail.

- Human SNP maps have been used successfully to identify genes that contribute to disease using whole genome association studies. Whole genome association involves testing cohorts of affected individuals for SNPs distributed across the genome and comparing the results with unaffected controls. The workshop participants agreed that developing a whole genome SNP map for this type of study is premature for the rhesus primarily because animal numbers may be too small to reach valid conclusions using this approach. Rather, emphasis should be placed on quantifying the effect of factors that could potentially limit the size of the genomic target needed for association studies and thus be useful for a targeted SNP-based approach. These factors include the ability to control the environment (e.g., the diet) of the animal, the pedigree structure and the ability to use genetic mapping (linkage analysis) to narrow the genomic target. The effect of these factors on the statistical power of association studies using SNPs should be examined.

- When sufficient sequence information is available on a representative number of animals, and the optimal size of a rhesus SNP map is better understood through pilot experiments, specific genotyping assays should be designed and applied to a large representative sample of animals from the National Primate Research Centers and other major sources of rhesus.

- In parallel with all genotyping experiments, investigators should phenotype the animals using standardized criteria and should derive immortalized cell lines from each animal.

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