



Nonhuman Primate Evaluation and Analysis

Part 2: Report of the Expert Panel Forum on Challenges in Assessing Nonhuman Primate Needs and Resources for Biomedical Research



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1. Introduction and Background

Nonhuman primates (NHPs) serve as critical animal models for many research areas, including infectious diseases; social, cognitive, and behavioral health; reproductive biology; regenerative medicine; aging and neuroscience research. The National Institutes of Health (NIH) provides support for NHP breeding colonies, facilities, and other research resources to facilitate the effective use of NHPs by NIH grantees as well as intramural scientists. This support is provided through grants and cooperative agreements administered by the Office of Research Infrastructure Programs (ORIP) within the Office of the Director as well as through other grants, cooperative agreements, and contracts administered by individual NIH Institutes, Centers, and Offices (ICOs).

Ensuring an adequate supply of NHPs to sustain research progress has been an ongoing challenge, with periodic shortages and surpluses being experienced at various times over the past several years. The NHP Evaluation and Analysis was conducted by ORIP to provide the NIH and the research community with an improved understanding of the demand for and supply of NHPs within the United States, with particular emphasis on ORIP-supported NHP resources, as these programs support research across the NIH. The results will also aid the NIH in determining the best strategy to pursue with regard to NHP research resources and capabilities in order to facilitate execution of NIH's research programs.

Part 1 of the NHP Evaluation and Analysis¹ assessed the capabilities of current major suppliers of NHPs and associated research services, and projected future needs based on a consideration of multiple factors, including historical usage trends by NIH extramural and intramural investigators, historical use at the seven NIH-sponsored National Primate Research Centers (NPRCs), qualitative or quantitative forecasts of future use by NPRCs and other NHP centers or commercial suppliers, and a survey of extramural NIH awardees. Part 1 of the study also identified, via the survey of awardees, key technologies of importance for NHP research; factors that influenced investigators' choice of NHP research facility to perform their studies; and problems that investigators encountered in obtaining NHPs or related research services that delayed their research, altered their experimental design, or influenced the conduct of their research.

The results from Part 1 of the study emphasized the importance of the NPRCs and other NIH-sponsored NHP centers as a significant source of NHPs and related services for NIH-sponsored investigators, particularly among those investigators located at institutions that do not maintain their own NHP facilities. The results also indicated current shortages and projected future high demand for and consequent shortages of rhesus macaques and marmosets as well as possible future increased demand for baboons. Infectious disease and behavioral and systems neuroscience research were, in general, the major drivers of NHP demand, particularly in regard to demand for rhesus macaques. Physical infrastructure limitations of the NPRCs were identified as barriers to increasing NHP supply to meet the expected future demand for NHPs. Problem areas specifically identified as impacting on NHP use included the high cost of animals, direct funding caps on grants as well as administrative cuts to budgets that reduce the number of animals able to be used and may adversely impact the statistical power of studies, and lack of peer reviewers with NHP expertise in NIH study sections.

2. Conduct of the Expert Panel Forum

To augment and expand upon the findings of Part 1 of the study, which were derived from historical analyses, supplier interviews, and user surveys, an expert panel forum was convened by the NIH on "Challenges in Assessing Nonhuman Primate (NHP) Needs and Resources for Biomedical Research."

¹ [Nonhuman Primate Evaluation and Analysis, Part 1: Analysis of Future Demand and Supply, NIH Office of Research Infrastructure Programs, 2018.](#)

The forum was conducted August 23-24, 2018 and brought together program officers from the NIH ICOs that sponsor the majority of NHP studies, leading researchers who use NHPs and represent a broad spectrum of scientific areas, and NHP resource managers from the academic, government, and commercial sectors. The objectives of the meeting were to:

- Forecast the future uses of NHPs in biomedical research
- Discuss and determine the scientific advances that are driving the future research
- Define the relevant and emerging NHP models that will be required for future biomedical advances
- Assess the capabilities of the existing resources and their ability to adapt to future needs, including an examination of the timeframe needed for expansion and, if expansion is not possible, what additional resources or infrastructure would be required
- Address the challenges in the resource planning process

The forum was designed with the assistance of an organizing committee comprised of experts in NHP research and resource management and was intended to examine demand and supply from the perspective of each of the three groups of attendees: program sponsors who broadly generate demand based on their funding priorities, researchers who have specific NHP needs, and resource managers who must manage their breeding colonies and provide specialized populations and research capabilities to meet the needs of researchers. The discussions and potential solutions identified by forum participants were further evaluated by the organizing committee after the conclusion of the meeting and synthesized into a set of key recommendations for NIH consideration. The members of the organizing committee, including short biographies, are provided in **Appendix A**.

The meeting agenda and list of participants are provided as **Appendix B**.

3. Outcomes from the Expert Panel Forum

Key outcomes from the expert panel forum are summarized below. Minutes of the meeting are provided as **Appendix C**.

3.1 Institute Forecasts

In the infectious disease area, the National Institute of Allergy and Infectious Diseases (NIAID) expects continuing high demand for Indian-origin rhesus macaques, particularly specific-pathogen-free (SPF) animals, and cynomolgus macaques. For certain studies, animals will need to also be prescreened to ensure that they have had no exposure to flavivirus, cytomegalovirus (CMV), or enteric pathogens, which will limit the number of animals that can be used. Chinese-origin rhesus macaques are primarily needed for studies of radiation/nuclear countermeasures and would be imported. There is also a potential increased demand in the future for baboons, especially SPF animals, and the existing NIH-sponsored colonies may require expansion to meet this need. Vaccine studies will require larger animals to allow for blood draws, and large numbers of animals will be needed for trials of products that must be developed under the Animal Rule.² Unexpected increased needs for NHP studies are also possible, associated with potential new outbreaks of Ebola, Nipah virus, Middle East Respiratory Syndrome, and Lassa virus. It was noted that other species might be substituted in the future for Indian-origin rhesus macaques, but bridging studies would be needed to establish comparability of data in these new species,

² The Food and Drug Administration (FDA) Animal Efficacy Rule (also known as the Animal Rule) applies to development and testing of drugs and biologicals to reduce or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic agents (chemical, biological, radiological, or nuclear [CBRN] substances), where human efficacy trials are not feasible or ethical. Further details are provided in the FDA's [Final Guidance for Industry: Product Development Under the Animal Rule, October 2015](#).

with prior work completed in rhesus macaques. NIAID is currently funding some intramural research in this area, but additional funding would be needed to establish any resulting new animal models in other laboratories. Encouraging researchers to employ a new NHP model is another challenge, as investigators prefer to remain with their current models, and funding for validation studies to move to a new model are scarce.

The National Institute of Mental Health (NIMH), National Eye Institute (NEI), and National Institute on Aging (NIA) all anticipate increasing use of marmosets and identified specific applications that may additionally increase demand for other species. NIMH projected a need for increased marmoset availability across multiple research areas. In the case of NEI, it was noted that an NHP model of neuronal regeneration in the retina will be needed to support the Institute's Audacious Goals Initiative, although the species for this model is still to be determined. NIA expects the use of marmosets as a model of aging (to include development of a transgenic model of Alzheimer's disease), and, in particular, noted that studies of aging will require 6- to 7-year-old marmosets, which are particularly difficult to obtain at present.³ In addition to marmosets, NIA is interested in the use of African green (vervet) monkeys as another potential model of Alzheimer's disease.

The future direction of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is uncertain due to the ongoing development of a new strategic plan, but at present the Institute expects to increase its efforts on preclinical development of contraceptives, which will in turn drive an increase in NHP use.

The National Institute on Drug Abuse (NIDA) noted that their studies currently use primarily rhesus macaques, but no major change in future use is foreseen at this time. The National Heart, Lung, and Blood Institute (NHLBI) similarly noted that their current studies primarily involve rhesus and cynomolgus macaques but did not indicate any changes in future use. The National Institute of Neurological Disorders and Stroke (NINDS) noted that the Institute does not prioritize any specific animal model, and future NHP demand will be driven by the applications submitted by investigators and prioritization of projects for funding through the peer review process.

3.2 Challenges

Forum participants described many of the same challenges to NHP research that were identified in the previously completed analysis of demand and supply, in several cases providing additional details and examples in which constraints had prevented important studies from being performed. Among these challenges were:

- *Animal Shortages.* Marmoset shortages were widely reported that are impacting both intramural and extramural research programs supported by NIH. Shortages are due to the relatively small number and size of existing colonies in relation to generally increasing demand for this species in neuroscience research and high interest in development of transgenic marmoset models. There are unique challenges associated with expansion of marmoset colonies due to limited expertise within the U.S. and a need to establish standardized housing, nutrition, and care for marmoset colonies. While some small colonies exist within the NPRCs and some universities, historical efforts to create larger scale marmoset colonies have failed. Maintaining necessary genetic diversity in existing small breeding colonies was also noted as a challenge. Regarding rhesus macaques, supply problems include low availability of infants for developmental studies and cycling females for inclusion in general studies and those involving women's health. In

³ NIA previously conducted a workshop in 2017 on the use of marmosets for aging research: [Marmosets as a model for biology of aging research, August 25-28, 2017 Washington DC.](#)

addition, there are insufficient numbers of CMV-negative and other herpes virus-free rhesus macaques for vaccine, organ transplant, immunology, and cancer research studies, as these colonies require distinct breeding strategies and housing. Inadequate numbers of serotyped and genotyped animals were also noted as a limiting factor. Looking forward, it was noted that competing demand from emerging Chinese contract research organizations and increasing challenges in air transport are significant threats to the future availability of imported cynomolgus macaques. It was also noted that the recently established Coalition for Epidemic Preparedness Innovations, an alliance between the Gates Foundation and foreign partners to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics, will place additional demands on NHP resources for vaccine development, potentially further exacerbating shortages.

- *Limitations of NIH Award Mechanisms.* Current NIH award mechanisms do not provide sufficient funds and/or flexibility to adequately support NHP research. The R01 activity does not provide enough funds or time to allow for long-term longitudinal studies (e.g., infant development and effects of aging that require more than 5 years). Utilizing sufficient numbers of animals for challenge studies often requires funds above the typical R01 level. A good grant mechanism for NHP model development and preliminary data acquisition is also lacking: The R21 activity⁴ does not provide sufficient funds to support exploratory NHP studies, and R01 and other grant applications are limited by the need for supporting preliminary data. Although the R24 activity⁵ may be used for model development, it is primarily supported by ORIP, which requires development of models that are relevant to two or more Institutes or Centers (ICs). In general, the activity codes lack the flexibility to accommodate unpredicted increases in NHP costs, such as those associated with acquisition of specialized populations of animals that are in short supply (e.g., SPF Indian-origin rhesus macaques, Mauritian-origin cynomolgus macaques). Finally, funding for P51 awards⁶ used to support the NPRCs has been flat over several years and, owing to inflation, does not allow for recovery of the actual cost of the resources.
- *Infrastructure and Space Limitations.* Current NPRC and NHP Resource Center facilities need revitalization and expansion to provide for colony growth and flexibility to provide new types of resources as well as to update aging infrastructure. Many academic centers involved in infectious disease research also lack adequate quarantine space, which can delay larger studies for months. Limited access to animal biosafety levels 3 and 4 facilities also impacts the ability to undertake infectious disease studies, particularly any long-term studies, which can be cost prohibitive. The lack of a major primate facility located in the Northeast U.S. was also cited by several researchers as a problem that hinders their access to NHPs.
- *Peer Review and Award Practices.* Researchers using NHPs expressed concern regarding inadequate expertise of study section reviewers on the value and use of NHP models, and there is a perceived bias of reviewers toward rodent models even when there is little evidence for the validity of these models. Researchers who serve on NIH study sections indicated observing these actions firsthand. There are frequently reviewer concerns around animal numbers in NHP applications, which is a consequence of the tight budget limits when including NHP work. Researchers also noted the additional adverse impact on NHP studies that results when there are post-peer review administrative cuts to awards.

⁴ R21 Awards: Research Project – Exploratory/Developmental Grants

⁵ R24 Awards: Research Project – Resource-Related Research Projects

⁶ P51 Awards: Research Program Projects and Centers – Primate Research Center Grants

In addition to these previously identified challenges, several new areas of concern were noted by participants:

- **Scientific Barriers:**
 - The lack of high-quality reference genomes for several NHP species is a barrier to progress: The current draft annotation of the rhesus macaque genome was generated by automated methods and has a large number of errors, but support to improve the annotation of this genome through manual curation is lacking. Sequencing for reference genomes of other NHP species, including annotation, has also not been adequately resourced. Embargoes on the release of genome sequence data into publicly available databases hinders progress.
 - Standardized methods for collecting and reporting phenotypic data are needed to move many research fields forward. Studies are constrained by a lack of correlation of genetic variations with phenotype as well as a lack of standardized nomenclature for and collection of data on basic phenotypes.
 - There are limited numbers of NHP reagents available: Most of the developed reagents are for rhesus macaques and are not useful for other NHP species. Similar reagents for other NHP species are needed.
 - All scientific research areas identified an on-going need to train the next generation of researchers and support staff in the use of NHP models and to provide support for their continued development. The concern was a loss of scientific expertise within the U.S., which would have a negative impact on U.S. biomedical research.
- **Limitations on Exploiting Emerging Transgenic NHP Models:** New transgenic NHP models may be developed in the next 3 to 5 years, but to expand these lines from the initially developed animals into larger colonies and phenotypically characterize them to the point where the models become useful to the larger research community will take several more years and require additional investments in infrastructure.
- **Commercial Supplier Reliability.** The quality of rhesus macaques available from commercial suppliers was questioned by some researchers, particularly in regard to behavioral studies that require animals raised in normal social settings. It was also noted that large commercial NHP suppliers have a financial incentive to retain animals in-house in order to maximize revenue by providing NHP services, versus selling animals to external researchers; and long-term commitment to maintenance of colonies is also an issue. From a financial perspective, it was suggested that rhesus macaque colonies are the only colonies that can be commercially sustained on a large scale due to the current demand and high selling price for these animals, which are largely driven by HIV/AIDS research; breeding colonies for other NHP species require subsidies by NIH to be financially sustainable.

3.3 Key and Emerging Technologies and Needs in NHP Research

ICO program officers and researchers identified a number of technologies that are currently in use and are expected to increase in importance in NHP research in the near future. Among these, several are of particular importance as they cut across numerous areas of research and were noted by multiple participants:

- Genomic sequencing and genotyping of NHPs to define new disease models, as well as expanded use of “-omics” technologies (e.g., single cell transcriptomics, metabolomics, lipidomics)
- Genomic editing, using CRISPR/Cas9, TALENS, or Zinc finger nucleases to create new NHP models of diseases and test gene manipulation methods to correct genetic defects *in vivo*

- Use of advanced imaging and biomarkers (e.g., positron emission tomography biomarkers) as diagnostic tools and for use in longitudinal studies
- Automated tools for behavioral monitoring and measurement in both cage-based and colony settings
- Expansion of major histocompatibility complex (MHC) and Fc genotyping to multiple NHP species for infectious disease and transplantation research
- Assisted reproductive technologies (ART) to support expansion of both genetically modified and conventional disease models

Additional technologies that were identified specifically with respect to neuroscience and behavioral research included:

- Use of viral vectors and nanoparticles for gene editing and drug delivery
- Image-guided brain surgery
- Long-term single neuron recording for analysis of activity during social interactions
- Use of optogenetics and chemogenetics for neuronal cell and circuit manipulation
- Real-time neurochemical sensors
- Use of induced pluripotent stem cell transplantation methods as treatments for neurodegenerative diseases

In general, participants thought there need to be adequate NHP resources available to allow preclinical testing of the safety and feasibility of potential vaccines and therapies before translation to the human clinic, when such testing is scientifically required. It was noted, however, that there is a need to train young investigators in the care of NHPs and how to work with them in translational or preclinical studies, as the pool of skilled researchers is limited. In addition, participants identified several scientific areas where new requirements are emerging that will drive future needs for specific species and specialized populations, including:

- Use of Mauritian-origin cynomolgus macaques for tuberculosis and other infectious disease research
- Use of New World monkey models for xenotransplantation studies
- Expanded studies of developmental programming in pregnant females (beyond the typical focus on the cardiovascular system)
- Use of CMV and herpes virus infection-free animals for transplantation studies and studies of congenital infection

3.4 Potential Solutions

Forum participants offered a number of potential solutions to the challenges that have been identified. While participants did not explicitly prioritize all of the potential solutions that were discussed, the following areas were deemed to be of particular importance: (1) improving communication within the NHP research community, (2) expanding rhesus macaque colonies, (3) expanding production of and access to marmosets, (4) establishing cynomolgus macaque colonies, (5) overcoming limitations of NIH award mechanisms, (6) enhancing the utility and value of existing NHP colonies, and (7) promoting training in NHP research. Further details of potential solutions for each of these areas are provided below:

- *Improving Communication.* Multi-faceted approaches are proposed to improve communication within the national NHP research community:
 - Creation of a formal trans-NIH NHP working group to promote NHP models and allow identification of initiatives involving NHP research that are being considered by multiple ICOs

- would improve projections on future needs and demands on resources. This may also promote data sharing, sharing of limited resources, and combined initiatives.
- NIH should encourage the establishment of an annual interagency “NHP Summit” involving NIH, other Health and Human Services agencies (e.g., the Biomedical Advanced Research and Development Authority, and the Centers for Disease Control and Prevention), Department of Defense medical research agencies, and other major sponsors of NHP research to promote a national solution for sustainment of a critical mass of animals and expertise in NHP models and methodologies.
 - NIH should improve the reporting of planned NHP use in NIH applications which, together with the ability to easily search and report on NHP use in the internal NIH information, management and planning system (IMPAC II), would allow NIH to provide suppliers with more useful projections of future demand to facilitate NHP production planning. Applicants currently must identify the species and total NHPs to be used, but consistent inputs on age, sex, and other special requirements (e.g., reproductive, genetic, and/or phenotypic status), including proposed use during the award period (e.g., numbers per year) have not been collected. Implementation would require NIH to make changes to standard application instructions and forms; technically this is possible. Projections resulting from analyses of application data could be communicated to suppliers in aggregate.
 - Improve communication on NHP availability and available infrastructure and expertise to allow more efficient use of existing animals and improve understanding among current and prospective NHP researchers of the resources that are available.
 - Unique identifiers to track individual animals and link them with data that has previously been collected on them could eliminate unnecessary rework and expense (e.g., sequence data, serology results, specific testing, etc.). A [Research Resource Identification Initiative](#) supported by NIH may assist in this process.
 - A central system to communicate animal needs and availability would promote efficient use of limited resources. A revamped “animal locator” system from the NPRC Consortium recently completed beta testing. This system, which resides behind a firewall, may provide a conduit for NHP researchers and resource suppliers to communicate animal needs and availability in a secure manner.
 - Establishment of a national consortium for NHP breeding colonies, similar to the current NHP pathology consortium (the Primate Pathology Database Collaborative) would also promote sharing of information on available resources within the NHP research community. This could be built off the existing Breeding Colony Management Consortium Working Group established by the NPRCs.
 - Promote tissue and organ sharing of existing biobanks at the NPRCs. This program distributes thousands of tissues from multiple sites each year, but many investigators are unaware of this resource. The availability of a tool to search for specific types of tissue would increase the value of this resource. Biobank expansion may be needed.
 - Promote existing visiting scientist programs at the NPRCs to increase awareness of these programs within the NHP research community. These programs allow external scientists to perform studies at shared laboratory facilities at any of the seven NPRCs.
 - *Expanding Rhesus Macaque Colonies.* Rhesus macaques, particularly SPF and CMV-free animals, remain in high demand. Their use in infectious disease studies, particularly those under the Animal Rule⁷, necessitate continued breeding. (Projections of suppliers provided during Part

⁷ See FDA [Final Guidance for Industry: Product Development Under the Animal Rule, October 2015](#).

1 of the NHP Evaluation and Analysis suggest that colonies should be expanded by 10% to 25% to keep pace with current and projected future needs.)

- *Expanding Production of and Access to Marmosets.* NIH should promote a decentralized solution for marmosets (i.e., smaller breeding colonies maintained locally at performing research organizations), but this approach should be supported by a strong network of users to develop evidence-based standards for care, communicate lessons learned, promote proper husbandry, and promote exchange of animals or gametes to maintain genetic diversity. The creation of more colonies will first require expansion of one or more centralized breeding colonies within established NHP centers to create a stock of breeding pairs that can be transitioned to external organizations to start up their local colonies. NIH should assist by increasing support to central breeding colonies as well as providing resource grants to institutions that have the expertise, capacity, and willingness to expand their existing marmoset colonies. A genetic management plan is needed for marmosets similar to the species survival plans used by zoos.
- *Establishing Domestic Cynomolgus Macaque Resources.* NIH should establish domestic colonies of cynomolgus macaques, including both Mauritian- and non-Mauritian-origin animals, to protect against predicted future constraints on imported animals. Genomic characterization of cynomolgus macaques is needed to establish a standard genotype to be used as the basis for colony development, since animal responses vary greatly depending on their origin. NIH supported researchers who work with cynomolgus macaques should be enlisted to assist with this effort.
- *Overcoming Limitations of NIH Award Mechanisms.* Proposed solutions for NIH to implement included:
 - Consideration by NIH for expanded use of IC-specific NHP resource grants or contracts to support institute-specific needs (similar to current Office of AIDS Research-sponsored SPF colonies that employ U42 awards and to the NIAID-funded breeding contract with Alpha Genesis), as well as multi-ICO support in areas of overlapping interest. Development of a CMV/herpes-free Indian rhesus macaque colony is one potential application of this approach. The use of contracted breeding colonies may leverage industry strengths in large-scale production and quality control. New model development also needs to be a component of IC strategic planning.
 - Increasing funding for NHP resource awards (e.g., P51, P40, or R24 grants) to increase capacity at NPRCs and NHP centers; construction grants should also be considered to renovate and expand infrastructure at NHP centers (NPRCs and other universities), with matching funds provided from the host institute. This may also include providing funding to maintain a “Strategic NHP Reserve” of Indian-origin rhesus macaques, in order to provide surge capability for unpredictable disease outbreaks or other similar requirements.
 - Utilizing the P01 mechanism⁸ to promote NHP model development.
 - Increasing the \$500,000 cap on annual direct costs in R01 awards that utilize NHPs.
 - Expanding research resource grants to support development of reagents that are specific to major NHP species beyond rhesus macaques.
 - Allowing flexibility in the timing of grant start dates to facilitate synchronization of studies with the birth season in rhesus macaques, in order to improve access to infant animals.
 - Providing supplemental or short-term funding within ICOs to support unforeseen costs associated with NHP acquisition.
- *Enhancing the Utility and Value of Existing NHP Colonies.* Proposed solutions included:

⁸ P01 Awards: Research Program Projects and Centers – Research Program Projects

- Initiating whole genome sequencing of U.S. colonies (both rhesus macaques and marmosets) or, alternatively, establishing a standardized set of genetic markers and incorporating these into a genotyping chip that can be used to characterize all animals. Implementing this solution will need a national program with centralized genome sequencing and bioinformatics support, including capabilities for genome assembly and annotation, and standardized genetic databanks that are made broadly available to the research community with NIH-enforced timelines for public data release. A consortium approach to this effort may be appropriate. The availability of high-quality genomic data would allow studies of phenotype-to-genotype associations and genotype-to-phenotype transitions and would allow identification of naturally occurring mutations that may lead to new models of behavioral disorders and other diseases.
- Establishing centralized facilities for NHP breeding technology, genomic editing, and transgenic animal production. This solution would enable efficient use of expertise and resources and ensure good animal husbandry practices to protect genetic diversity. It should also provide long-term stable funding for highly trained staff who are skilled in *in vitro* fertilization and embryo transfer, an essential requirement to achieve high breeding success rates and rapid colony expansion. Centers could also provide technical support to all NHP researchers and promote best practices and sustainment of a skilled workforce through training of technicians and young investigators.
- Increasing the utilization of the Caribbean Primate Research Center (CPRC). A solution needs to be implemented to facilitate the transfer of animals from the CPRC to the mainland, which currently can only be accomplished through third parties. The CPRC has existing under-utilized infrastructure that could be used to develop an Assisted Reproductive Technology core facility.
- Promoting the use of alternative minimally invasive research techniques to reduce morbidity and enable the productive re-use of animals. The Animal Welfare Act and Institutional Animal Care and Use Committees limit the number of invasive procedures that can be performed on an animal over its lifetime, but animals employed in non-terminal studies may otherwise be useful for additional studies.
- *Promoting Training in NHP Research.* Potential solutions to expand the pool of appropriately skilled NHP researchers included encouraging specific NHP-centric training through Research Career Development Awards (K series) as well as possibly incorporating training components into U42⁹ or R24 awards.

3.5 Additional Considerations and Future Directions

There was a general concern among many forum participants that the U.S. is in danger of losing its international leadership in NHP research to countries such as China and Japan that are emphasizing NHP research with government-driven initiatives, and that urgent action is needed. The current U.S. NHP resources and the expertise that they represent could not be rebuilt if they are lost, and loss of these capabilities would have impact on the ability to identify and develop new medical products to improve health, respond to emerging infectious disease threats, and protect against CBRN¹⁰ threats to national security and public health. NIH needs to determine what critical mass needs to be sustained to protect intellectual property, meet current research needs, and maintain responsiveness to emerging health needs. NIH also needs to consider what the most cost-effective approach strategies are to balance NHP supply and demand, explore different business models to meet NHP supply requirements, and decide

⁹ U42 Awards: Animal (Mammalian and Nonmammalian) Model – Animal and Biological Materials Resource Cooperative Agreement

¹⁰ CBRN: Chemical, Biological, Radiological or Nuclear

whether a top-down approach using resource grants as a means to subsidize NHP research is the best approach to maintain NHP availability and affordability. The outcomes from the forum may be used to develop concepts for presentation to NIH ICO Advisory Councils, which could ultimately lead to new Funding Opportunity Announcements, as one of several possible approaches to implement solutions to current NHP resource challenges.

In general, it was also observed that the NHP research community needs to work together to better communicate the predictive value and costs of NHP models to ICO Program Officers and the research community as a whole, so that the best model for any particular area of research is used based on science rather than animal availability, funding, or other driving factors. This is in keeping with the general principle that science should drive funding rather than funding driving science.

3.6 Key Recommendations

In considering the potential solutions identified by forum participants, the following were identified as key recommendations by the organizing committee:

1. Establish a trans-NIH NHP working group to coordinate and harmonize management approaches and funding of NHP studies; evaluate and communicate future resource needs to resource managers; promote sharing of limited NHP resources; and consider co-funding initiatives among ICOs to more effectively leverage funds. The working group should include NIH representatives of NHP research portfolios and NHP resource sponsors and should meet regularly throughout the year. In addition, an interagency NHP Consortium should be established in coordination with other federal agencies that perform or sponsor NHP research. This consortium should meet annually to exchange information on planned research and development programs that involve NHPs; evaluate issues affecting national demand for and supply of NHPs; develop a national strategy to ensure creation (as needed) and sustainment of those NHP resources deemed to be critical to national interests; and promote the implementation of this strategy.
2. Increase funding levels for existing NHP resource and resource-related grants (e.g., P51, P40, U42, R24 grants) to enable improvements to infrastructure and provide support for expanding colonies to meet demand. This increase is needed to rectify the effects of flat budgets that have resulted in an approximately 20% decline in terms of real dollars that has occurred in the funding of these resource grants over the past 15 years, as well as address the additional demand on remaining NHP centers that occurred both as a result of the closure of the New England National Primate Research Center, and increasing demand in general.
3. Develop and implement a plan to determine the genetics of all domestic NHP colonies supported by the NIH. The plan needs to include strategies to make the data and accompanying information accessible to the research community. Whole genome sequencing of NHPs is considered critical to maximize the use of animals and should be the ultimate goal based on the maximum value of the information obtained as well as the declining cost of whole genome sequencing. The availability of sequence information will provide a large return on investment, identifying new opportunities for disease models. A working group of geneticists should be employed to determine the most cost-effective method to complete sequencing and devise a plan for this endeavor.
4. Provide NIH resources to expand existing colonies of rhesus macaques, including SPF and enhanced SPF colonies, by 10% to 25% in order to meet growing demand for Indian origin animals for research across the NIH enterprise. Expand current resources for specific NPRCs/NHP Centers to facilitate screening and specific breeding and housing of CMV and other herpes virus-free rhesus macaque colonies.

5. Expand current NIH-sponsored marmoset colonies, as part of trans-NIH projects, to provide breeding pairs that can be used to seed satellite colonies for use at investigator's institutions. Concurrently with this effort, establish a working group of experts in marmoset colony maintenance to establish standards for marmoset diet and animal husbandry and develop a plan to maintain genetic diversity across colonies. All recipients of breeding pairs from central colonies must commit to adherence to the standards established by the working group, including participation in the genetic diversity plan as a condition of receipt of animals.
6. Establish domestic breeding colonies of cynomolgus macaques in coordination with other federal agencies. Develop and implement a plan to establish one or more domestic colonies of cynomolgus macaques for use in federally funded research and development. As an initial step, convene a focus group of primary stakeholders involved in NIH- and other federally funded projects using this species in order to better define the colony size, origin, genetic characteristics and other details that are needed to meet research requirements. This analysis should consider the needs of projects supported by various federal funding mechanisms including grants, cooperative agreements, contracts, other transaction agreements, and intramural awards.
7. Provide support for the development of species-specific reagents, assays, and technologies for multiple NHP species, beyond those for rhesus macaques. Additional reagents, assays, and technologies are needed to advance science in those fields that rely on other NHP species.
8. Provide training opportunities to sustain and expand the pool of researchers and support staff who are skilled in the use of NHPs. Continued scientific advancement of NHP-related research is dependent on having appropriately trained and skilled personnel. Personnel who understand the various NHP models are critical to selecting the proper model to address the proposed scientific question.

Appendix A – Expert Panel Forum Organizing Committee Members and Biographies

Expert Panel Forum Organizing Committee Members

Jon E. Levine, Ph.D. (Chair), is the Director of the Wisconsin National Primate Research Center and Professor in the Department of Neuroscience at the University of Wisconsin-Madison. For the past 40 years, he has studied the neuroendocrine regulation of gonadotropin releasing hormone neurons. Dr. Levine's research has also focused on the molecular and cellular mechanisms by which ovarian steroids exert their physiological and behavioral effects in the brain, including the negative feedback mechanisms that maintain homeostatic control within the reproductive axis as well as the positive feedback actions of steroids that trigger preovulatory gonadotropin surges. His recent work has made use of newly developed mutant mice and non-human primate models to analyze the cell signaling mechanisms that mediate negative and positive feedback actions of estradiol, the role of steroid hormone receptors and kisspeptin neurons in the timing of puberty, and as the effects of estrogens on energy homeostasis and body weight.

Dr. Levine completed his B.A. at Oberlin College in Oberlin, Ohio, and his Ph.D. from the University of Illinois, Champaign-Urbana. He completed postdoctoral training at the Oregon National Primate Research Center & Oregon Health Sciences University and joined the faculty at Northwestern University in Evanston, Illinois in 1984, remaining there as Professor in the Department of Neurobiology and Physiology until 2010. While on the faculty at Northwestern, Dr. Levine served as Director of the Program in Biological Sciences (1999-2006) and as Director of a NIH-sponsored Training Program in Reproductive Biology (1991-2010). Dr. Levine has served as Editor-in-Chief of the journal *Frontiers in Neuroendocrinology*, and as a member of the Steering Council for the Office of Research on Women's Health at the NIH. He is an active member of numerous professional societies including the Endocrine Society, Society for Neuroscience, and the Society for the Study of Reproduction.

Christian R. Abee, D.V.M., M.S., DACLAM, is the Doctor R. Lee Clark Professor and Chair of the Department of Comparative Medicine, University of Texas MD Anderson Cancer Center, Michale E. Keeling Center for Comparative Medicine and Research. He has served as a Principal Investigator of NIH grants and contracts continuously since 1980. He directs several national research resources, including the Squirrel Monkey Breeding and Research Resource, the Owl Monkey Breeding and Research Resource, the Rhesus Monkey Breeding and Research Resource, the Specific Pathogen Free Baboon Research Resource, and the National Center for Chimpanzee Care. He also served as a member and as chair of the NIH Comparative Medicine Review Committee. Dr. Abee has served on the National Research Council's Institute of Laboratory Animal Medicine Council, the Association for Assessment and Accreditation of Laboratory Animal Care Council on Accreditation, and the Board of Directors of the National Association for Biomedical Research; is a past president of the American College of Laboratory Animal Medicine (ACLAM) and the Association of Primate Veterinarians; and has served on the National Scientific Advisory Boards of four national primate research centers. Dr. Abee has devoted much of his career to improving the care of laboratory animals through advancing laboratory animal medicine and improving animal facilities by creating facility designs that address the natural history of the species to be housed. He has served as an editor of both editions of *Nonhuman Primates in Biomedical Research* and has authored many articles and chapters.

Dr. Abee received his DVM from Texas A&M University in 1971. He completed a postdoctoral fellowship and training program in comparative medicine at Wake Forest University School of Medicine in 1974, and began his career in laboratory animal medicine as a Research Scientist and veterinarian at the Tulane National Primate Research Center. In 1975, he became a diplomate of the ACLAM. Dr. Abee became Director of Animal Health and Resources at University of South Alabama College of Medicine in 1979, where he later became a department chair and Distinguished University Professor. In 2005, Dr. Abee moved to the University of Texas MD Anderson Cancer Center to become the Doctor R. Lee Clark

Professor and Chair of the Department of Veterinary Sciences (now the Department of Comparative Medicine) and Director at the Michale E. Keeling Center for Comparative Medicine and Research.

Jon D. Hennebold, Ph.D., is Professor and Chief of the Division of Reproductive & Developmental Sciences at the Oregon National Primate Research Center (ONPRC). He is also Professor in the Departments of Obstetrics & Gynecology and Physiology & Pharmacology in the Oregon Health & Science University's School of Medicine. Dr. Hennebold also served as the Director of the ONPRC Assisted Reproductive Technologies (ART) Core, which supports research activities involving nonhuman primate studies of reproductive biology. Since arriving at the ONPRC in 2000, Dr. Hennebold has focused on defining the cellular and molecular processes occurring in the ovary that are necessary for female fertility. Dr. Hennebold has advanced our understanding of the molecular processes that are critical in primates for ovulation as well as the development, function, and regression of the corpus luteum. To correct issues of efficiency and health risks associated with current infertility treatments and to provide for assayable markers of high oocyte competency, Dr. Hennebold studies how diet and elevated androgen levels impact the development and release of a fertilizable oocyte. The Hennebold laboratory is also interested in ARTs and the use of recently developed gene editing tools, such as CRISPR or TALENs, for creating relevant models of human disease. He currently serves as the lead for a project funded through the NIH Somatic Cell Genome Editing consortium that aims to develop nonhuman primate reporter expressing animals that can be used to assess the efficiency and specificity of recently developed genome editing technologies.

Dr. Hennebold received his Ph.D. at the University of Utah School of Medicine in Cell Biology & Immunology. His postdoctoral training in reproductive physiology was also at the University of Utah in the Department of Obstetrics & Gynecology. Dr. Hennebold has served on several grant review panels and journal editorial boards. He was a member of the Board of Directors for the Society for the Study of Reproduction and now serves as a member of the Society's Development Committee. He is also an active member of the Endocrine Society and the American Society of Reproductive Medicine.

Sallie R. Permar, M.D., Ph.D., is Professor of Pediatrics, Immunology, and Molecular Genetics and Microbiology at Duke University School of Medicine. Dr. Permar is a physician scientist focusing on the prevention and treatment of neonatal viral infections. She leads a research laboratory investigating immune protection against vertical transmission of neonatal viral pathogens, namely HIV and cytomegalovirus (CMV), using human cohorts and nonhuman primate models. Dr. Permar has made important contributions to the development of vaccines for prevention of vertical HIV transmission, defining both innate and adaptive immune responses that are associated with protection against infant HIV acquisition. Moreover, Dr. Permar is leading the development of HIV vaccine strategies in preclinical maternal/infant nonhuman primate models and clinical vaccine trials in infants. Dr. Permar has also contributed to understanding of determinants of perinatal CMV transmission and postnatal infection in preterm infants, developing the first nonhuman primate model of congenital CMV infection now used to define the immune correlates of protection necessary to guide vaccine development.

Dr. Permar has a Ph.D. in Microbiology/Immunology from Johns Hopkins Bloomberg School of Public Health in Baltimore, an M.D. from Harvard Medical School and completed her clinical training in pediatric infectious diseases at Children's Hospital in Boston. She has received several prestigious early-stage investigator awards, including the Presidential Early Career Award in Science and Engineering, was inducted into the American Society of Clinical Investigation in 2016, and became a Fellow of the American Academy of Microbiology in 2018. She is also an institutional and national leader in physician-scientist training, serving as the Associate Dean of Physician-Scientist Development at Duke University Medical School and was selected by the Association of Medical School Pediatric Department Chairs as the next Director of the Pediatric Scientist Development Program in 2019.

James Pickel, Ph.D., is the chief of the National Institute of Mental Health Transgenic core facility and a Staff Scientist at the National Institutes of Health. The transgenic core facility provides services to NIH neuroscience investigators in several intramural institutes and collaborates with NIH and extramural investigators to develop new techniques for the use of transgenic animals in medical research. Dr. Pickel has created unique mouse embryonic stem cells to produce transgenic rodent lines. He has developed techniques to produce transgenic rats, including a panel of neuronal-subtype-specific CRE recombinase lines in collaborations with National Institute on Drug Abuse investigators. Most recently he has made transgenic marmosets that transmit the transgene through the germline. He continues to develop techniques that will enable the genetic manipulation of nonhuman primates. These animals will be used to investigate the development and function of the nervous system in normal and disease states.

Dr. Pickel received an A.B. from The College of William and Mary in English literature. He received his Ph.D. from The University of Alabama in Birmingham in Microbiology, working on the genetics of the development of lymphocytic stem cells. He completed postdoctoral training in developmental neurobiology at the NIH where he studied the expression of genes that are activated in neural stem cells.

Appendix B – Expert Panel Forum Agenda and Participants

Challenges in Assessing Nonhuman Primate Needs and Resources for Biomedical Research Expert Panel Forum

Purpose of the Meeting:

Nonhuman Primates (NHPs) are critical models used for studying human diseases as well as basic physiology, developmental processes and behaviors. Because of their similarity to humans in physiology, neuroanatomy, reproduction, development, cognition, and social complexity, they are in many cases the best model. For these reasons, NIH has made investments over the years in establishing NHP resources and supporting scientific research using NHPs. Examples of research areas in which NHP models are essential encompass: Infectious diseases including HIV/AIDS; neural, mental, and social development and associated disorders; vision studies; metabolic disorders; reproductive studies; and regenerative medicine. Regulated pre-clinical efficacy and toxicity studies in NHPs often precedes clinical trials in humans and cannot be replicated any other way. New models currently in demand are those for studies in Alzheimer's disease and related dementias, models to address drug addiction including opioid abuse and models of genetic disorders, where gene editing may be used to study human disease counterparts. NHP resources supported by NIH collectively provide NIH-funded investigators access to NHPs; these resources continue to develop NHP models of human disease, expanding the array of models. Ensuring an adequate supply of NHPs to sustain research needs is important to NIH and the research community. Taking into consideration that these resources require time and infrastructure investment to expand, and to gauge current and emerging scientific areas requiring NHP models and the expansion capabilities of the existing resources, an NHP Evaluation and Analysis of current and future demands was undertaken. This assessment will provide the research community and NIH with an improved understanding of the demand for and supply of NHPs within the United States. The expectation is that these results together with the discussion at the forum will inform NIH where the needs are, where resources are needed, and how to reprioritize resources, if necessary. The analysis included 4 components:

- A review of the capabilities of major U.S. NHP service providers
- A retrospective analysis of NHP use by NIH grantees and intramural NIH animal census from 2013-2017
- An analysis of historical NHP use data and forecasts of future demand for NHPs from major NHP service providers, and definition of their operational characteristics
- Results of a survey of NIH-sponsored NHP users to characterize current and future areas of science and demand

The results of these initial efforts suggest a potential trend in increased demand and need for macaques and marmosets in the coming 5 years, as well as potential increased demand for baboons. The fifth component of this project is to convene an expert panel to assess the state of the science and its impact on NHP resources. Although alternatives to the NIH-sponsored centers and colonies exist for some species and types of research, the NIH-sponsored centers serve as a major resource for many NIH-supported investigators, especially those who lack access to an NHP-capable facility within their own organization.

Panel Objectives:

- Forecast the future uses of NHPs in biomedical research
- Discuss and determine the scientific advances that are driving the future research
- Define the relevant and emerging NHP models that will be required for future biomedical advances
- Assess the capabilities of the existing resources and their ability to shift with future needs; Examine what timeframe is needed for expansion and, if expansion is not possible, what additional resources or infrastructure would be required
- Address the challenges in the resource planning process

Conference Organizing Committee:

- Jon Levine (Chair), Wisconsin National Primate Research Center, WI
- Chris Abee, MD Anderson, TX
- Jon Hennebold, Oregon National Primate Research Center, OR
- Sallie Permar, Duke University, NC
- James Pickel, National Institute of Mental Health, NIH

NIH Organizing Committee:

- Sheri Hild, Division of Comparative Medicine (DCM), Office of Research Infrastructure Programs (ORIP), Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), National Institutes of Health (NIH), Bethesda, MD
- Miguel Contreras, DCM, ORIP, DPCPSI, NIH, Bethesda, MD
- Desiree Vonkollmar, ORIP, DPCPSI, NIH, Bethesda, MD
- Lola Ajayi, ORIP, DPCPSI, NIH, Bethesda, MD
- Alan Feister, Leidos, NIH contractor

Forum Schedule:

Day 1

8:00 – 8:30 Registration

8:30 – 9:00 Introduction and Welcome
Stephanie Murphy, DCM Director, ORIP, NIH

NIH Initiatives and the Planning Process
Sheri Hild, DCM, ORIP, NIH

- **Challenges in Predicting Future NHP Needs**
 - Insufficient information from Institutes and Centers (ICs) regarding their NHP needs (intramural and extramural);
 - Unexpected demands due to global threat of a new disease or natural hazards
 - Insufficient knowledge of different NHP models – using the best model to answer the question.
- **Examples of Successful Initiative Planning**
- **Directive to the Panel**

9:00 – 12:00 Session 1: Future NIH Research Priorities
Session Co-Chairs: Sheri Hild and James Pickel

Objectives: (1) Are institute priorities shifting towards (or away) from studies that are likely to require use of nonhuman primates? (2) How do ICs Funding Opportunity Announcement (FOA) practices (e.g., topic or activity code selection) effect the use of nonhuman primates? (3) What can individual ICs do to better forecast their future needs for NHPs and share this information with the resource funders and providers? (4) How can ICs be more attentive in considering resource availability in future initiatives? (5) How can ICs communicate their future resource needs?

9:00 – 10:30 NIH ICs and Programs NHP Priorities

- National Institute of Allergy and Infectious Disease: William Dowling, Kristy Kraemer, Nancy Miller
- Office of AIDS Research: Jay Radke
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development: David Weinberg, Daniel Johnston
- National Institute of Mental Health: Andrew Rossi, Jannie Simmons, Elizabeth Murray
- National Eye Institute: Martha Chapelle Flanders
- National Institute of Neurological Disorders and Stroke: Jim Gnadt, Daofen Chen
- National Institute on Aging: Manuel Moro
- National Institute on Drug Abuse: Roger Little; Steve Grant
- National Heart, Lung, and Blood Institute: Cynthia Dunbar
- Office of Research on Women's Health: Elena Gorodetsky, Chyren Hunter

10:30 – 10:40 Break

10:40 – 12:00 Expert Panel and Open Discussion

- The panel will discuss the questions listed under the objectives of this session. This includes the perspective of the NIH Representatives.

12:00 – 12:30 LUNCH

12:30 – 5:30 Session 2: Scientific Factors Impacting on Demand for NHPs and NHP-Associated Services

Session Co-Chairs: Jon Levine and Jon Hennebold

Objectives: (1) Is the demand for certain NHP species changing (increasing or decreasing)? (2) How will requirements for segmentation of animals (genetic requirements, Rigor & Reproducibility, Sex as a Biological Variable (SABV), or other factors that create requirements for specific sub-populations of animals) affect future demand? (3) How will emerging technologies, such as gene editing, effect demand for NHPs? (4) Are there new research techniques or specialized equipment or facilities that are likely to become more important for NHP research in the coming 5 years? (5) Are there particular skills or facilities that are currently in short supply? (6) What research capabilities should NIH-sponsored NHP centers provide because they aren't readily available from other sources?

12:30 – 3:10 Breakout Group Discussion by Research

(To include panel experts in the research field, NIH Representatives in research area, resource experts and Out-brief Preparation, with break as desired by each group).

- **Infectious Disease Research**

Chair: Sallie Permar

- Guido Silvestri
- Ruth Ruprect
- Koen Van Rompay
- Joanne Flynn
- Miti Kaur
- Keith Reeves

- **Neuroscience/Behavioral Research**

Chair: James Pickel

- Michael Platt
- Cory Miller
- Marina Emborg
- Xiaoqin Wang
- Karen Parker
- Guoping Feng

- **Reproductive, Developmental, Endocrine & Metabolism Research**

Chair: Jon Hennebold

- Ted Golos
- Lisa Miller
- Laura Cox
- Anthony Chan
- Jon Hennebold
- Suzette Tardif

- **Stem Cell, Regenerative & Transplantation Medicine**

Chair: Kyle Orwig

- Martha Neuringer
- Kyle Orwig
- David Cooper
- Dixon Kaufman
- Stuart Knechtle

3:10 – 3:30 Break

3:30 – 5:30 Session 2 Plenary: Breakout Group Out Briefs and Open Discussion
Include overlapping technologies or factors that drive all fields: genome editing; genetic diversity versus inbred traits; defining specific pathogen free resources; issues that create resource “bottlenecks”; translational science.

5:30 – 5:45 Day 1 Closing Remarks and Adjournment
Stephanie Murphy

Day 2

8:00 – 11:30 Session 3: Factors Impacting on Supply of NHPs for NIH-Sponsored Research
Session Co-Chairs: Chris Abee and Skip Bohm

Objectives: (1) What are the expectations for continued future supply of imported NHPs from China or other countries, and what (if any) effects are expected on industry and the competition between industry and academia for supplies of domestic NHPs? (2) Should, existing colonies be expanded, or other additional domestic colonies be established to augment commercial sources, and what additions are suggested for increasing the value/impact of existing colonies? (3) Aside from simply increasing production, are there other actions that NIH-sponsored NHP centers can take to make animals more accessible to grantees (e.g., increasing external sales)? (4) Should animals from NIH-sponsored NHP colonies be made more accessible to not-for-profit and industrial users? (5) How can NIH ICs contribute information to improve the forecast and planning process for future NHP needs?

8:00 – 8:10 Use of NHP Studies for Decision Making in Viral Vaccine Development at Pfizer
Phillip Dormitzer

8:10 – 9:45 Expert Panel Discussion

Panel members:

- Pablo Morales
- Boris Predovich
- Jay Kaplan
- Suzette Tardif
- Bob Adams
- Rob Norgren
- Phillip Dormitzer
- Alphonse Cisar

9:45 – 10:00 Break

10:00 – 11:30 Session 3: Open Discussion

11:30 – 12:00 Closing Remarks/Highlights
Stephanie Murphy

Adjourn

**Challenges in Assessing Nonhuman Primate (NHP) Needs and Resources for
Biomedical Research Expert Panel Forum
August 2018
Participant List**

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Lola Ajayi

Student Trainee, ORIP/NIH

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Appendix C – Expert Panel Forum Minutes

**National Institutes of Health (NIH)
Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
Office of Research Infrastructure Programs (ORIP)**

Challenges in Assessing Nonhuman Primate Needs and Resources
for Biomedical Research

Expert Panel Forum

August 23–24, 2018

Building 31, Room 6C10
NIH Main Campus
Bethesda, MD

Report¹¹

Forum Day 1

Introduction and Welcome

Stephanie Murphy, Director, Division of Comparative Medicine (DCM), ORIP, NIH

Stephanie Murphy opened the meeting by welcoming participants, speakers, and panelists and acknowledging the NIH Organizing Committee, Conference Organizing Committee, and others who assisted in developing the agenda and providing logistical support.

Nonhuman primates (NHPs) serve as critical animal models for many research areas, including infectious diseases; social, cognitive, and behavioral research; reproductive biology; regenerative medicine; aging; and neuroscience research. Multiple NIH Institutes, Centers, and Offices (ICOs) provide support for NHP breeding colonies, facilities, and other research resources to facilitate the effective use of NHPs by NIH grantees and intramural scientists. Ensuring an adequate supply of NHPs to sustain research progress has been an ongoing challenge, with periodic shortages and occasional surpluses occurring at various times over the past several decades.

The NHP Evaluation and Analysis was conducted by Leidos to provide the NIH and the research community with an improved understanding of the demand for and supply of NHPs in the United States, with a particular emphasis on NIH-supported NHP centers and resources. The results also will help the NIH determine the best strategy to pursue with regard to NHP research resources to facilitate execution of NIH's research programs. The study used multiple methods to evaluate future demand and supply, owing to the uncertainties associated with any single method, and was composed of several distinct components, including convening an expert panel (i.e., this forum) to assess the state of the science and its impact on NHP resources.

NIH Initiatives and the Planning Process

Sheri Hild, DCM, ORIP, NIH

Sheri Hild explained that NHPs are used because of their similarity to humans in terms of physiology, neuroanatomy, reproduction, development, cognition, and social complexity. NHP studies precede clinical

¹¹ Meeting minutes were prepared by The Scientific Consulting Group under Contract Number GS-07F-431AA.

trials. NHPs are used in research supported by almost all NIH ICOs. The NHP Evaluation and Analysis identified a number of challenges in predicting NHP needs for future research, including:

- Insufficient information from ICOs regarding their intramural and extramural NHP needs and usage (e.g., how and when their needs are communicated to NHP suppliers)
- Unexpected demands due to the global threat of a new disease or natural hazard (e.g., Zika virus)
- Insufficient knowledge of different NHP models (e.g., are investigators using the best model to answer their research question?)

With regard to NIH planning, concepts and/or ideas for an initiative come from many sources. These include NIH and ICO strategic plans, program officers identifying a gap in a research field, scientific workshops, input from the scientific community (e.g., through Requests for Information), the NIH ICOs contributing concepts for the Common Fund, advisory groups, and Congressional funding. After describing the concept-to-award process at the NIH, Dr. Hild offered the following examples of effective initiative planning:

- Increased pressure for genetically modified mouse models led to the formation of the Mutant Mouse Resource and Research Centers (MMRRC). The MMRRC started in 1999 with funding through cooperative research agreements (U42) that involve the development of animal model resources. In May 2001, the MMRRC launched its public website and began accepting applications for submissions of strains to the repository. In October 2002, the MMRRC's first strains became available to requesting investigators.
- Increased demand for swine models led to the creation of the National Swine Resource and Research Center (NSRRC). The NSRRC was established in 2003 to develop the infrastructure to ensure that biomedical investigators across a variety of disciplines have access to critically needed swine models of human health and disease, including specific pathogen-free (SPF) animals, the capability of genetic manipulations, a central repository, and a resource for best practices.
- SPF macaque colonies support HIV/AIDS research. Macaque monkeys are the primary model used for HIV/AIDS research. The presence of certain viruses in the monkey experimental subject can confound the results of AIDS-related investigations. Since 2000, cooperative agreements have supported the development of SPF macaque colonies as resources for AIDS research.
- The Common Fund program, Somatic Cell Gene Editing (SCGE), is a recent example of a large program that identified and included resources in its overall plan. Many common and rare diseases are due to changes in the genetic code, and genome editing technologies may pave the way for potential treatments for these diseases. The SCGE plans to expand the number of genome editing tools available to researchers; develop delivery systems that can target the cells of specific organs and tissues in the human body efficiently; design new assays for testing the safety and efficacy of editing and delivery tools; and distribute the knowledge, methods, and tools that have been developed through this program to the scientific community. The overall program included requests for rodent and large animal centers for developing and testing SCGE tools. Support for these resources was considered essential for the program to achieve its objectives.

Dr. Hild concluded her remarks by outlining the following six objectives for the panel:

- Forecast the future uses of NHPs in biomedical research.
- Discuss and determine the scientific advances that are driving future research efforts.
- Define the relevant and emerging NHP models that will be required for future biomedical advances.
- Assess the capabilities of the existing resources and their ability to shift with future needs.
- Examine what timeframe is needed for expansion, and if expansion is not possible, what additional resources or infrastructure would be required.
- Address the challenges in the resource planning process.

In response to a question about outputs from this forum, Dr. Hild explained that a summary will be generated based on the proceedings. Any recommendations, guidance, suggestions, and so forth from this forum are for NIH's use and for use by the research community. The summary from this forum will be made publicly available. Additionally, the NHP Evaluation and Analysis report currently is in draft form and will be finalized, after which it will become publicly available.

Session 1: Future NIH Research Priorities

Session Co-Chairs: Sheri Hild and James Pickel

NIH ICs and Programs NHP Priorities

National Institute of Allergy and Infectious Diseases (NIAID)

William Dowling, Kristy Kraemer, Nancy Miller

William Dowling presented the research priorities and challenges of NIAID's Division of Microbiology and Infectious Disease; Division of AIDS; and Division of Allergy, Immunology, and Transplantation. Due to the breadth of NIAID's mission, a large number of unique NHP models are needed, including models for dozens of infectious diseases, radiation exposure, and transplantation research. A key issue affecting each division is the high demand for NHPs in NIAID intramural and extramural programs. The main species used are cynomolgus and rhesus macaques with an emphasis on SPF Indian origin rhesus. Other species include African green monkeys, pigtailed macaques, baboons and marmosets, although these are used at lower numbers than the macaques. Few extra animals are available and thus shortages occur at times of unexpected demand, such as when an emerging disease outbreak occurs. In addition, SPF animals are in high demand and several models have additional prescreening requirements, further limiting the number of appropriate animals. Certain of these extra requirements, such as cytomegalovirus (CMV) negative animals or animals with particular major histocompatibility complex (MHC) types, severely restrict the number of animals that can be put on a study. Limited facilities, including biocontainment laboratories and quarantine areas, are additional issues.

Proposed solutions to the need for more animals include increased breeding of NIH-owned animals for purchase by principal investigators (PIs) at a subsidized price, support for increased breeding at the National Primate Resource Centers (NPRCs), expanding current colonies to provide breeders for a new colony, and using other species in new disease models. Funding remains an issue.

A participant noted that new model development is one of the most difficult areas for which to obtain support, and investigators are reluctant to change models. Dr. Dowling responded that NIAID's preclinical services program supports development of proof of concept research in alternative models for infectious disease research. Additional funds would be required to transition models to other research laboratories.

Office of AIDS Research (OAR)

Jay Radke

Jay Radke provided an overview of the role and responsibilities of OAR, which works across the NIH and with the scientific and HIV clinical communities to establish HIV/AIDS research priorities and develop strategic plans for HIV research. OAR also ensures that funds are invested in these priority areas and helps address emerging needs, primarily by convening stakeholders and encouraging collaborations to address new public health challenges. The Office works to coordinate the scientific, budgetary, legislative, and policy components of NIH HIV/AIDS research.

HIV/AIDS expenditures for research involving NHPs averaged more than \$200 million per year between 2012 and 2017. HIV/AIDS funds supporting the NPRCs since 2012 have averaged \$50 million per year. OAR also maintains funds that can allow the Office to respond to emergency needs relevant to the HIV/AIDS pandemic as well as natural disasters that impact HIV/AIDS research centers. An example of this is the recent use of emergency funds to support the rebuilding of macaque colony facilities at the University of Puerto Rico, which were devastated by Hurricane Maria.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

David Weinberg, Daniel Johnston

Daniel Johnson gave an overview of the Institute and examples of NHP research. There are 12 extramural branches of NICHD that conduct a wide range of research focusing on reproductive tissues. For example, the Fertility and Infertility Branch conducts basic studies involving NHPs, including preserving male fertility after cancer therapy. The Contraception Research Branch is involved in research to develop such products as male contraceptive agents. The Pregnancy and Perinatology Branch, one of the pillars of NICHD, conducts considerable research on placenta-fetal development during primate pregnancy. The Obstetric and Pediatric Pharmacology and Therapeutics Branch conducts research on extending the use of pharmaceutical products. The Maternal and Pediatric Infectious Disease Branch has been very interested in studying the effect of the Zika virus on the reproductive tract, during pregnancy, and in children. The Child Development and Behavior Branch is another large NICHD branch that uses NHPs in research, as do the Intellectual and Development Disabilities Branch and the Pediatric Growth and Nutrition Branch.

In response to questions, Dr. Johnson planned to determine which species predominates in NICHD's NHP research and how many studies in NICHD's child development portfolio are making use of transgenesis or genomic editing models in NHP studies. When asked whether NICHD has contract-based use of NHPs, Dr. Johnson responded that NICHD uses NHPs in its contraceptive biological testing facility. A medicinal chemistry facility is also available to synthesize compounds for testing. Although he anticipates that use would increase for contraceptive development, NICHD is heading into strategic planning activities and establishing future research priorities, so this will have to be confirmed.

National Institute of Mental Health

Andrew Rossi, Janine Simmons, Elisabeth Murray

Andrew Rossi explained that NIMH's use of NHPs is primarily for studies of neurobiological processes underlying cognitive, social, and affective behaviors and their development. NIMH typically uses rhesus macaques, although some studies use marmosets and other types of NHPs. The number of monkeys used per study is relatively small (between six and 12 monkeys), although the retention of NHPs usually is longer because of the time commitment to train the animals to perform particular cognitive tasks as well as the high number of longitudinal studies. Other areas of research using NHPs include:

- Cellular and molecular mapping
- Anatomical and functional connectivity studies
- Interventions development
- Studies that seek a mechanistic understanding of neuroscience methodology used in humans
- Development of PET radioligands
- Safety and efficacy studies of HIV anti-viral therapies

The future direction of NIMH research using NHPs includes:

- Molecular tool development for next-generation cell and circuit manipulation (e.g., optogenetics and chemogenetics)
- Gene editing
- High-channel count probes for neural recording and stimulation (including closed-loop systems)
- Fine-grained, quantitative behavioral phenotyping in naturalistic settings
- Appropriately powered studies to investigate sex as a biological variable (SABV)
- Development of high-fidelity telemetric recording systems (for central and autonomic nervous systems) to combine with measurements of behaviors in laboratory-based and naturalistic settings
- Use of combined methods to identify neural mechanisms (e.g., neuronal recording plus circuit manipulation)

A participant commented about improving molecular genetic tools in NHPs, noting that differing amounts of resources are available for each species, with far more resources available for rhesus monkeys than other species, which may make researchers default to using rhesus monkeys. The level of annotations of the genome is far better in rhesus monkeys than in other species. In some cases, the participant noted, the development of genome annotation tools for a few prioritized species is being promoted because, even though such annotations in NHPs lag behind rodents, rhesus monkeys are ahead of all of the other species.

Dr. Rossi responded that a critical mass of users for a particular species is necessary to support the development of vectors or a targeted molecular tool. He noted that this critical mass has occurred with marmosets now—and with rhesus monkeys to a certain extent—but not with other species of NHPs.

A participant asked how many multi-ICO grants are funding NHP studies. Dr. Rossi responded that a typical investigator-initiated application goes to only one given ICO, but that there also are trans-NIH initiatives, such as the BRAIN initiative. Although the majority of grants do not have co-funding, there may be shared resources at the grantee level.

Another participant noted that the amount of available funding will drive NHP use and will be the key factor in predicting future NHP needs.

National Eye Institute (NEI)
Martha Chapelle Flanders

Martha Chapelle Flanders reviewed NEI's mission and its vertebrate animals portfolio, focusing on extramural research involving central vision. Currently, most research grants involving central visual pathways, eye movements, and the retina—all part of central vision—use monkeys (primarily macaques), followed by mice. NEI also is interested in using other NHP species (mostly marmosets) to take advantage of their smaller size, cost, and breeding characteristics. NEI is supporting an “Audacious Goals Initiative RFA-EY-17-003” that uses NHPs to develop translational models of diseases of the retina and its central projections, which are similar to human anatomy and physiology and thus better mimic human eye diseases. For example, NEI is interested in exploring how to regenerate cells (e.g., photoreceptors and retinal ganglia cells) that malfunction in macular degeneration and glaucoma. Compared to mice, the retinas of NHPs have more cell types and can process more complex visual information, making them important to vision research.

Dr. Flanders noted the following challenges and suggestions:

- It is increasingly difficult to import NHPs, necessitating a robust local supply.
- Breeding programs and transgenic animal production should be centralized to efficiently use expertise and resources and ensure good animal husbandry practice to protect genetic diversity.
- It seems sensible to develop shared laboratory facilities that could be used by investigators interested in NHP research, especially those who are unable to establish NHP laboratories in their institutions.

National Institute of Neurological Disorders and Stroke (NINDS)

Jim Gnad, Daofen Chen

Daofen Chen gave an overview of the use of NHPs in NINDS' research projects. NINDS is a major [NIH Blueprint for Neuroscience Research](#) ICO, with an annual budget of about \$1.9 billion, of which 86 percent funds extramural research. Currently 98 of the 2,847 active multiyear grants using animals employ NHPs, representing a total annual cost of approximately \$54 million. NHP research project awards represent approximately 3.4 percent of all NINDS animal research grants or about 2.7 percent of all the institute's research project awards. Although NINDS' NHP research projects use small numbers of animals, they involve long-term longitudinal studies and require complicated invasive neurosurgical procedures, behavioral training paradigms, and chronic neural recordings and assessments. The NHP research grants have been made to 18 public and 33 private organizations that are able to provide highly skilled NHP neurosurgical, electrophysiology, and biomedical engineering technical support. Currently, the NINDS intramural program is not conducting any significant neuroscience research using NHPs. NINDS suggestions for future planning include (1) improving reporting and data collection through NIH IMPAC II to help meet the challenges in predicting future NHP needs and (2) designating specific staff scientist/specialist positions for NHP research to help stabilize the technical workforce and preserve capacity in critical NHP research, including systems and behavioral neuroscience.

National Institute on Aging (NIA)

Manuel Moro

NIA supports about 170 aged rhesus macaques at three NPRCs. The animals range in age from 16 to more than 25 years of age. Aging colonies are more expensive to maintain, and rising per diems, inflation, and flat budgets have caused aged monkey populations to erode. The monkeys are available for a reduced fee to NIH-funded investigators studying any area related to the aging process. More funding is becoming available for Alzheimer's disease and related dementia issues.

Other priorities and areas of interest include:

- Marmosets as models of aging, including expanding the aged marmoset population, new initiatives to characterize the aging process in older marmosets, and potential Alzheimer's disease models (transgenic marmosets)
- African green monkeys (*Chlorocebus aethiops*) as potential models of Alzheimer's disease

National Institute on Drug Abuse (NIDA)

Roger Little, Steve Grant

Roger Little explained that two divisions of NIDA are the primary users of NHPs: drug treatment and medical complications. Rhesus monkeys are the biggest component of NIDA's portfolio. Although NIDA does not anticipate many changes in this general trend, the Institute has been discussing the benefits of marmoset research, in particular their shorter gestation times, lifespans, higher fecundity, and ability to study these highly social animals' behavior.

Barriers to using NHPs include fast-rising prices and not having sufficient rhesus females with the necessary sexual maturity available for research. Solutions to barriers, according to Dr. Little, include:

- Increasing the supply of rhesus monkeys, which will cost money
- Creating an NHP biobank so organs and tissues are available for pilot studies
- Using resources from a human brain bank network
- Creating a genetic data repository with reference data for all of the species used; make data discoverable so that secondary data analysis can be done.

National Heart, Lung, and Blood Institute (NHLBI)

Cynthia Dunbar

Cynthia Dunbar gave an overview of NHLBI's extramural primate usage and intramural primate programs. NHLBI is interested in systems to better track which grants use NHP models. NHLBI's extramural primate usage is relatively low for the size of the Institute. Alternative large animal models for cardiovascular disease research are focused on pigs, dogs, and sheep. Rhesus and cynomolgus macaques have a higher usage than baboons and pig-tailed macaques. The current availability of primates has not been a major issue for NHLBI-supported investigators. The Institute does not have marmoset programs, a species that is presently in high demand. NHLBI currently has a large intramural primate program with 152 rhesus macaques housed on the Bethesda campus. The program supports multiple intramural NHLBI PIs, collaborating PIs across other Institutes, and collaborating extramural investigators. The intramural program is focused on developing high-intensity cell and gene therapies for cardiovascular and blood diseases, including hematopoietic stem cell transplantation and treatment of blood diseases. Pluripotent stem cell regenerative medicine models also are a focus for cardiac, bone, hepatic, and stromal cell regenerative models. Unfortunately, many individual centers have shut down due to the high cost of maintaining these programs.

Office of Research on Women's Health (ORWH)

Elena Gorodetsky, Chyren Hunter

Elena Gorodetsky explained that the goal of the NIH's Sex as a Biological Variable (SABV) policies is to maximize how well NIH-funded research considers the documentation and reporting of sex differences or influences. This consideration may increase reproducibility of research studies; lack of reproducibility is a current research issue. Currently, male animals dominate many research areas—including research on conditions that affect females more than males—and many studies do not report the sex of the subjects or have inconsistent reporting of sex-specific findings, making it challenging to correctly interpret results. As a result, the NIH made plans to enhance reproducibility and balance sex in cell and animal studies with the goals of enhancing rigor, providing transparency, filling knowledge gaps, maximizing return on investment, and supporting generalizability of the research findings. The NIH SABV Policy became effective in January 2016 and requires that, without strong justification from the scientific literature or preliminary data, SABV will be considered in the research designs, analyses, and reporting in vertebrate and human studies. SABV in studies can be accounted for in many ways. Through various grant mechanisms, ORWH has supported SABV in NHP research in the areas of menopause and biodermography of aging and the "four Cs" of studying sex to strengthen science: consider, collect, characterize, and communicate.

Expert Panel and Open Discussion

The following points were made in discussion:

- Participants discussed the number of NHPs NPRCs sell to outside institutions. Although the percentages vary by location, most colonies are dedicated to high-priority NIH research projects and meeting the objectives of NPRCs. NPRCs are designed to enable the experiments of core and affiliate scientists. Core scientist are central to the NPRC, whereas affiliates are external investigators, some of who may be at the host institution. The NPRCs include scientific

implementation units to either assist with or conduct experiments for investigators from other institutions. When considering where to sell surplus NHPs, NIH-funded studies are prioritized, followed by federally funded studies, nonprofits, and for-profit companies. Most of the scientists throughout the United States who do their work at NPRCs are NIH-funded investigators. Although the study-allocated NHPs are paid for by the individual investigator's grant (fee based on funding source), the majority of the research is conducted at the NPRC in collaboration with core scientists to leverage the available infrastructure.

- Attendees emphasized that the mission of NPRCs should be leveraged by fully utilizing their resources, including not only NHPs but also the intellectual resource of the investigators and the physical resources of the equipment. NPRCs should participate in the effort to expand the national marmoset colony to meet increasing demand, but existing award mechanisms do not provide sufficient funding. Participants suggested looking to the history of U42 mechanism that have been used to develop and support SPF macaque colonies for HIV/AIDS research. Collaboration with multiple ICOs would help with this endeavor.
- The ICOs do not have an effective way to track primate use, and attendees wondered whether NHP use could be incorporated as a specific part of ICOs' strategic plans. Although NHPs deserve consideration in their use and tracking, most ICOs' strategic plans usually do not include specific animal models but rather address specific diseases or conditions. However, the long time period needed to plan for NHP research may necessitate an exception to this rule.
- Although coding and tracking NHPs is technically simple, policy changes are needed before such structures can be implemented.
- NHP research requires special consideration with regard to information that is public because of issues with animal rights activists.
- Individual ICOs rarely have resource grants that can be used to address the logistical issues involved in NHP research.
- Attendees suggested the formation of a trans-NIH NHP working group to increase communication.
- Attendees asked about the possibility of a smaller-scale regional resource to provide animals to areas lacking NPRCs, such as the Northeast.
- As marmoset use increases, many locations may want to establish colonies, and marmosets can be housed and bred under relatively standard vivarium conditions. However, more cooperative approaches between institutions may be necessary to ensure that animals are available; standardized approaches to diet, housing, and care are established; and colonies are appropriately managed to maintain genetic diversity.
- Knowledge of the number of marmosets in all institutions, including NPRCs and private and public universities, is more complete than for other species because, until recently, the marmoset research community has been small. The Marmoset Research Group of the Americas (MaRGA) has not been active for many years, but researchers are expressing interest in reinstating that organization, which could serve as a point for management, trading, and creation of a species survival plan similar to those used in zoos.
- A participant commented that NPRCs lack the flexibility to adjust to variable supply and demand. A bottleneck occurs when researchers request NHPs that are not available, which delays studies and increases costs to acquire NHPs.
- An attendee noted that a deeper issue is that needs for NHPs are driven by investigator-initiated applications, and the extent to which known limited resources prevent researchers from applying for grants is unclear. Another attendee commented that this affects applications *a priori* because young investigators have neither an established colony nor the preliminary data required to apply for high-risk, exploratory, important NHP research.
- An attendee commented that existing primate facilities need to be supported, because the infrastructure and veterinary care present in these facilities would be extremely difficult to rebuild.

- When asked how the process of obtaining NHPs has changed in the past few decades, several participants responded that their PIs suggest obtaining NHPs is possible, but the factor that makes investigators give up is the lack of institutional support. Centralized facilities are appealing because universities often are unwilling to support the necessary infrastructure. A participant commented that centralized facilities can implement a system for visiting scientists to ensure that appropriate care for the animals is part of the resource provided to investigators.
- A participant described an existing marmoset colony without the capacity to provide animals to outside researchers and noted that the NIH could help by providing resource grants to institutions that have the expertise and willingness to enlarge their colonies. The bottleneck applies not only to the actual animals but also to the expertise and training required to expand the use of such delicate animals. NPRCs have an obligation to provide the appropriate education to ensure that NHPs are cared for appropriately.
- An attendee cautioned that this group should assess whether the current demand for marmosets relates to researchers who want animals for a discrete study or want to set up their own colonies in many locations. Both are valid models that create different agendas for the resources in the community and potential NIH support.
- The current population of marmosets has stabilized, which should make it easier to predict how many animals will be available to outside investigators in the next few years.
- A participant suggested that investigators new to working with marmosets should “buy futures”—purchase breeding pairs that can be supported for 2 years while other infrastructure and expertise is put into place, resulting in a 30-animal marmoset colony by the time the center has been established. Current marmoset centers often dedicate their existing capacity to the grant application portfolio and those who will be actively using the colony through that mechanism.
- An attendee noted that infrastructure is the underlying issue, and such constraints dictate what the internal programs can do: requests from outside investigators are entertained, but by the time available animals are allocated based on the NIH prioritization guidelines, none remain for outside groups. The infrastructure aspect needs to catch up to the current demand before NPRCs can fulfill their objectives as providers of primates.
- Participants emphasized that the NIH should take a leadership role in developing a syndicate or network that would help investigators find needed NHPs more readily. NPRCs often are limited, although the quality of their animals may be more dependable; including commercial vendors in such a network may allow for more flexibility than government-only institutions. Another participant expressed disappointment that ICOs do not feel it is in their capacity to support outside researchers, especially since the NPRCs are an investment by all. The NIH should prioritize increasing that capacity so researchers can benefit from this resource.
- An attendee commented on the time needed to set up colonies, particularly for social or behavioral research because certain relationships and social hierarchies must be established.
- A participant proposed determining how many researchers are counting on the promise of transgenic marmosets, which may help answer a wide variety of scientific questions but also are decades away in terms of development.
- Attendees commented on the difficulty in fulfilling gene-editing initiatives when the number of animals available is insufficient, reducing the utility of the animal model. Another participant commented that the genomic editing revolution seems to be leaning toward somatic cell genomic editing in adult animals, or developing animals for acute studies rather than embryonic stem cell genomic editing and propagation of animals. The issue should be considered in that light, which provides a pressing reason to expand colonies. Attendees discussed the need to screen and build animal models for somatic cell editing, which requires time to breed and grow the animals. Small transgenic populations have been seen in Japan and at the Massachusetts Institute of Technology (MIT), but will require expanding and phenotyping, which will take time to complete.
- Participants emphasized the need to begin by genetically characterizing the animals to identify off-target effects and variants as well as perform quality control. Populations provided by outside

vendors may have unknown sources or genetics, so NPRCs should be able to provide very specific genetic characterizations as part of their mission. Another attendee suggested that characterization could apply in a number of ways, such as the health status, behavior, rearing, and other factors that fold into reproducibility. A participant noted that commercial vendors with high standards should not be completely ruled out, as they may be the only source for special populations.

- NPRCs have a mission to support emerging research, such as through pilot project programs that invite investigators to bring good ideas to those with monkey experience. Participants suggested that the NIH should be providing that information to young investigators who want to work in primate research.
- Participants discussed special populations or special requirements that may be difficult to acquire, particularly for investigators who are not based at an NHP research center. Such populations include SPF Indian-origin rhesus macaques and Mauritian-origin cynomolgus macaques. Investigators need these NHPs to gather preliminary data for their next grant submission, and although institutions often allow administrative supplement requests for unexpected increases in cost, such as those associated with challenging acquisitions, better mechanisms to procure such populations are needed.
- Attendees commented on the gap in mechanisms between recent discoveries—such as new naturally occurring models, or new opportunities, such as those emerging related to gene editing—and the long-term flat funding for NPRC base grants. Previously available grants used for capacity and housing are no longer available, some grants support only models that can be relevant to multiple ICOs, and there are no grant mechanisms to create a new model.
- A participant suggested that the NPRCs need strategic investment by the NIH to keep the NPRCs funded, as the NIH already has made a massive resource investment. Programmatic decisions that emphasize NHP research and initiatives clearly structured to use NHPs also are needed. Finally, the peer review system must include research colleagues who deem NHP research competitive for funding. Once these three arrangements are in place, scientific research for the sake of science should be able to occur fluidly, without additional costs or hurdles. The participant suggested that the logical solution to smooth the path would be to add a measure of flexibility and resources to ensure that the necessary research can be arranged.
- Attendees suggested that there is a great need for individual ICOs to dedicate their own resources toward this problem, specifically separating and designating part of their budget to release requests for applications (RFAs) for NHP research-centered applications dedicated to addressing Institute-specific health issues. Instead of obscuring the fact that the NIH uses NHPs in its research to avoid conflict, the attendee suggested that the ICOs should take the opposing tack and declare this type of research critically necessary, with the monetary support to back up such a position.
- Public-private partnerships, such as that between the NIH and Alpha Genesis, can effectively utilize the different expertise and benefits of each side, meet the needs of researchers, and provide for future support.

Session 2: Scientific Factors Impacting on Demand for NHPs and NHP-Associated Services

Session Co-Chairs: Jon Levine and Jon Hennebold

Session 2 Plenary: Breakout Group Briefs and Open Discussion

Neuroscience and Behavioral Research

Chair: James Pickel; Breakout Members: Michael Platt, Cory Miller, Marina Emborg, Xiaoqin Wang, Karen Parker, Guoping Feng

This breakout discussion focused on the needs, challenges, and opportunities in conducting neuroscience and behavioral research with NHPs.

The following needs were identified by the group:

- Serotyped NHPs.
- Genotyped NHPs. Whole-genome sequencing of entire colonies at multiple NHP facilities would identify genetic determinants of disease.
- *Is the demand for certain NHP species changing (increasing or decreasing)?*
 - The demand for NHPs to develop human disease models for studies of the following is likely to increase:
 - Harmonic processing and pitch perception.
 - Social communication.
 - Naturally occurring social and behavior deficits and abnormalities.
 - Candidate biomarkers and signaling pathways associated with such behavioral disorders as autism.
 - Marmosets have provided useful models in studies of behavior, social communication, and computational neuroethology. Computational neuroethology studies are developing methods for recording the behavior of single neurons over periods of up to 1 year.
- *How will requirements for segmentation of animals (genetic requirements, rigor and reproducibility, SABV, and other factors that create requirements for specific subpopulations of animals) affect future demand?*
 - The financial limit for R01s that support NHP studies should be increased to allow adequate power to analyze data on both sexes.
- *Are there new research techniques or specialized equipment or facilities that are likely to become more important for NHP research in the coming 5 years? What research capabilities should NIH-sponsored NHP centers provide because they aren't readily available from other sources?*
 - Bioinformatic support
 - Reproductive centers for breeding and distribution of NHPs for genomic editing studies
 - Centralized genomic editing cores

The following challenges were identified:

- Consideration of ethics in NHP studies is critical. Ethical considerations should be discussed at the national level, particularly for genomic editing studies.
- Opaque and unpredictable pricing of NHPs is a challenge.
- Shortage of NHPs is a limitation, particularly infants with developmental disorders.
- *How do ICOs' Funding Opportunity Announcement (FOA) practices (e.g., topic or activity code selection) affect the use of NHPs?*
 - The lack of top-down support (e.g., a national initiative) limits the development, updating, and dissemination of models of disease because of their cost. If such an initiative is implemented, the group recommended strategic planning sessions, a white paper, and partnerships with multiple ICOs.
 - Inflexible grant start dates are a challenge. Projects that involve NHPs should have flexible start dates.
 - Funding duration for NHP studies also should be more flexible to allow for measurement at different developmental time points.

- The current funding mechanisms lead to underfunding of NPRCs, with deficits recouped by PIs.
- Investigators also have difficulty maintaining animals on a per diem.
- Base grant awards are insufficient to accommodate emerging technologies. A more effective grant mechanism might be a P01 for NHP research, which covers the development of methods and technologies for this research.
- The \$500,000 limit for R01s might need to be re-examined because it limits investigators' ability to complete NHP studies at cost.
- R21 funding is not appropriate for NHP research. A different type of award is needed for developmental or exploratory NHP research with a duration of more than 2 years.

The following opportunities were identified:

- *How will emerging technologies, such as gene editing, affect demand for NHPs?*
 - NHPs are or could be important in studies of:
 - Induced pluripotent stem cell transplantation methods for new treatments for neurodegenerative diseases
 - Image-guided brain stereotactic manipulation in a variety of venues
 - PET biomarkers
 - Real-time neurochemical sensors
 - Genetic engineering of models of brain disorders
- *How can ICOs be more attentive in considering resource availability in future initiatives?*
 - For NHP species that are involved in research less often (e.g., the marmoset), their participation in research would require the development of adequate breeding colonies. An investigator at Johns Hopkins University established a self-sustaining colony, which can serve as an example for developing this type of resource.

Infectious Disease Research

Chair: Sallie Permar; Breakout Members: Guido Silvestri, Ruth Ruprecht, Koen Van Rompay, Joanne Flynn, Miti Kaur, Keith Reeves

Sallie Permar reported on the Infectious Diseases breakout discussion. The group converged on five challenges to be addressed and suggested solutions to be further investigated:

- Approaches to alleviate the long wait and/or increased cost for procuring NHPs for supporting funded studies are needed.
 - Potential solutions are to (1) incorporate flexible funding within existing mechanisms (e.g., P51s) that support the NPRCs; (2) establish supplemental or short-term funding within ICOs to support unforeseen costs or circumstances of the research/study, such as purchasing NHPs from outside vendors; and/or (3) increase the total budgets for NPRC awards (P51s) and investigator-initiated NHP research (R01s) to account for inflation.
- New science, technological advances, and improved methodologies in NHP research continue to evolve, but funding to support NHP pilot studies in the context of a larger research study is limited. In addition, a formalized structure to communicate the needs across NHP users is lacking.
 - Potential solutions are (1) recycling or reusing the same animals for unrelated studies to offset costs; (2) developing a database or tracking system of NHP use (on and off studies) across NHP Centers (NPRCs and others); (3) improving communications among NHP Centers (NPRCs and others) and researchers to coordinate general animal colony

breeding procedures (e.g., culling periods); and (4) providing funds for vivarium husbandry per diem cost for animals suitable for recycling.

- Because additional disease models are being developed, the demand for specialized NHP populations far exceeds the supply. As a minimum, infrastructure changes will be necessary to support new model development and validations. Example areas of model development needing attention include domestic breeding of cynomolgus macaques for tuberculosis research, procurement of Mauritian cynomolgus macaques for T-cell studies, and expansion of breeding CMV- and herpes virus infection-free animals for transplant and congenital infection research.
 - Potential solutions to support model development include (1) establishing new model development funding sources; (2) implementing a matching funds program within the ICOs that mirrors the NIH Clinical Translational and Service Awards program; (3) encouraging the ICOs to support specific models; (4) encouraging data sharing between researchers; and (5) providing funding to leverage the existing NPRC infrastructures to expand rhesus macaque breeding as demand increases.
- The ongoing need for NHP genetics, immunologic characterization, and reagent development primarily has been focused on the rhesus macaques and should be expanded to include other NHP populations.
 - Potential solutions are to (1) continue the NIH NHP Reagent Resource, which has been valuable to the research community and (2) expand the MHC and Fc region characterizations to other NHP populations.
- Trained NHP researchers are limited to support studies.
 - Potential solutions are to (1) establish a training program to maintain and increase the pipeline of the next generation of NHP researchers and (2) incorporate NHP training into the Research Career Development Awards (K series).

In discussion, the following points were made:

- The NPRC animal locator tool is underutilized and has been revamped to model the former Primate Supply Information Clearinghouse Newsletter, which was a communication mechanism that investigators could use to help meet their NHP needs. Beta testing the new version of the locator tool is in progress at the NPRCs. The next steps will need to determine the NHP allocation criteria and reinforce the security protocol for the website. The goal is to provide this service to the broader NHP research community, especially other NHP resource centers and universities.
- Recycling animals for experiments, which may not be an option at some institutions, will require Institutional Animal Care and Use Committee (IACUC) approval.
- The Animal Welfare Act of 1966 prohibits the use of animals in multiple surgical procedures, which will be indicated on the NPRC animal locator forms.
- Approximately 250 animals are recycled annually in commercial sector repurposing programs and would be a resource that the NHP Centers could leverage. Procurement costs are reasonable for animals reintroduced into the market, and educational gaps in academia also are being addressed.
- NIAID has been addressing the need to expand MHC and Fc region characterizations to other macaque populations (e.g., cynomolgus and pig-tailed macaques) and has funded two contracts: one to the University of Wisconsin-Madison (2004) and one to the Biomedical Primate Research Centre (2011). The technologies exist, and the information is available on a clearinghouse website, but members of the NHP research community would need to convey their needs to the ICOs.
- Although draft genomes generated using automated annotation processes (e.g., the National Center for Biotechnology Information) are useful, their accuracy must be reviewed and the annotation process completed manually. Funding to support NHP genome sequencing is needed. Precise genome editing would be a significant investment for the NIH.

Reproductive, Developmental, Endocrine, and Metabolism Research

Chair: Jon Hennebold; Breakout Members: Ted Golos, Lisa Miller, Laura Cox, Anthony Chan, Suzette Tardif

Jon Hennebold, as the chair for the group, listed the following emerging technologies important to reproductive, developmental, endocrine, and metabolism research on NHPs:

- Genome editing.
- Advanced imaging and biomarkers to allow for longitudinal studies, more powerful studies.
- Developmental programming will become a major focus to expand beyond the typical cardiovascular disease programming that occurs *in utero* or during the periconception period.
- Omics, such as genotyping for disease models, single cell transcriptomics, metabolomics, lipidomics.
- Automating and standardizing behavioral monitoring.

The group further identified the following needs and barriers:

- Animal availability, specifically cycling females, which allows for colony expansion and is important for developmental programming issues and developmental biology aspects.
- Breeding programs that allow adaptation to infectious disease during pregnancy.
- Infrastructure and space limitations, and aging facilities, which allow no room for expanding resources or investigating new areas or new directions. This makes it difficult to adapt to emerging areas and reduces flexibility in responding to emerging infectious diseases.
- Funding—
 - Administrative cuts to awards that are applied in council or post-review independently of consideration for the funding needs of specific animal models. For example, a 20 percent across-the-board funding cut will affect an NHP grant more severely than a mouse grant.
 - NHP expertise on study sections is lagging in certain cases; individuals with expertise are needed to understand the value of the model and appropriately evaluate the research.
 - Typical duration of funding does not allow for longitudinal or long-term development or aging studies; consideration of a more flexible grant model is needed.
 - The flat P51 budget has been very limiting with regard to what NPRCs can do, which also is important for infrastructure and flexibility considerations.
- Genetics, including reference standards, accurate annotations, characterized pedigrees, and the like.
- Publicly available databases are needed in which data are deposited in a timely manner.
- Lack of phenotype standardization in terms of genetic components is a barrier.
- NHP-specific reagents for multiple species are needed.
- Resources, resource sharing, and technical expertise also are a challenge.
- Assisted reproductive technology/in vitro fertilization (ART/IVF) is a critical need/issue moving forward; it allows for rapid expansion of disease models, whether genetically engineered or naturally occurring.

The group noted the following potential solutions:

- Construction grants; resources for infrastructure, maybe matching funding from the institution or host organization.
- A more unified front on promoting the value of the NHP model, which also will allow researchers to be responsive to individual ICO needs and emerging areas (e.g., Zika, opioids).
- Regarding study section grant funding, consideration of multi-ICO support of NHP research in overlapping areas of interest.
- Resource grants beyond the standard approach, resource grants available to develop reagents that are specific to different NHP species, or development of biobanks or databases for genomics, genetics, or phenotypic data.
- Different Councils and Institutes need to consider the effects of across-the-board budget cuts that result in cuts to the number of animals in a study and can affect the rigor and reproducibility that a study was originally approved to conduct.
- Ensure NHP expertise is available throughout all study sections.
- Participants discussed whether a centralized resource would be effective, including the following examples:
 - A centralized breeding resource where embryo transfers could happen, such as a genetically modified embryo, rather than having each entity housing 50–100 females
 - Centralized distribution of reagents or a network for reagents specific to various species
 - Centralized technical support for all NHP users in terms of best practices for housing, technical issues, and training

Stem Cell, Regenerative, and Transplantation Medicine

Chair: Kyle Orwig; Breakout Members: Martha Neuringer, Kyle Orwig, David Cooper, Dixon Kaufman, Stuart Knechtle

Kyle Orwig delivered the report of this discussion to the larger group of meeting participants, based on the preliminary questions suggested. The breakout discussion focused on research related to stem cell or organ transplantation, and gene therapy and immune system rejection and tolerance associated with those therapies.

The following needs were identified:

- *Is the demand for certain NHP species changing (increasing or decreasing)?*
 - NHPs are needed to develop human disease models for studies of transplantation and gene therapy.
- *Are there new research techniques or specialized equipment or facilities that are likely to become more important for NHP research in the coming 5 years?*
 - ART/IVF will be needed to support gene editing and the production of new animal models. ART/IVF resources and facilities exist but will need to expand to a wider range of locations. Currently, these resources require the maintenance of large colonies of female NHPs.
- *What research capabilities should NIH-sponsored NHP centers provide because they aren't readily available from other sources?*
 - Resources are needed to expand the study of novel mutations that might arise in NHP colonies. The Oregon NPRC, for example, has a Japanese macaque colony with unique mutations that offer an opportunity to learn about human disease. Resources, however, are lacking for the expansion of this colony to study the phenotypes.

- In general, high-quality, well-characterized breeding colonies are needed, particularly as the number of NHP disease models increases. These colonies need high-quality health histories and genotyping (particularly MHC typing for transplant research).
- Most NHP reagents are focused on the rhesus macaque. The development of similar reagents in other NHP species might benefit research on NHPs.
- A mechanism is needed to advertise biobanking resources available to the research community. For example, a Chinese rhesus resource is available at Tulane University.
- A mechanism is needed to improve clinical infrastructure and training for NHP research. Participants in the breakout session suggested employing U42 or R24 mechanisms for this purpose.

The following challenges were identified:

- Once models are developed, small, private NHP colonies will be created that are genetically inbred. A mechanism to ensure the genetic diversity of these colonies will be needed. For example, a mechanism could be developed to facilitate cross-breeding across different facilities.
- In general, the availability of NHPs is a limitation. The limited availability of SPF Indian-origin rhesus monkeys is a particular challenge for investigators conducting NHP research.
- Another challenge is that NHP research does not always translate to humans. A biobanking resource would help investigators determine the reasons for differences in NHP outcomes and human outcomes.
- In addition, the rate of translation into the human clinic is outpacing NHP research. For this reason, findings from mouse models frequently are moved directly to human trials. Infrastructure and funding are needed to enhance the pace of NHP research.
- *How do ICOs' FOA practices (e.g., topic or activity code selection) affect the use of NHPs?*
 - Current infrastructure and space for maintaining NHP models is inadequate. Funding beyond the traditional 5-year period is needed to maintain adequate infrastructure.
 - A full 5-year funding cycle would be needed to produce an NHP model and possibly phenotype a single animal. To make the model a resource for the community, longer term funding would be needed to expand and phenotype the model completely.
 - Animals also need to be monitored over a longer period to determine long-term outcomes of interventions beyond study endpoints. Long-term monitoring of NHPs will require more than a 5-year funding cycle.
- *Are there particular skills or facilities that are currently in short supply?*
 - Many young investigators are not trained in the care of NHPs and how to work with them in translational or preclinical studies. Training in this area will be necessary for effective NHP research.

The following opportunities were identified:

- *What can individual ICs do to better forecast their future needs for NHPs and share this information with the resource funders and providers?*
 - Discoveries made using NHPs that translate into effective human treatments should be tracked. The documentation of these successes would support the utility of NHPs in medical research.
- *How will emerging technologies, such as gene editing, affect demand for NHPs?*
 - Many stem cell, transplant, and gene therapy technologies are in the preclinical stages of development, presenting opportunities for NHP model development. The strengths of NHPs include larger size, immunological similarities to humans, and longevity.

- The emerging CRISPR-Cas9 genetic editing technology offers an opportunity to develop new NHP models with greater ease and precision for the purpose of testing relevant therapies.
- *How can ICOs be more attentive in considering resource availability in future initiatives?*
 - NHPs of different strains, even among rhesus monkeys, are available to researchers, but this is not clearly communicated to the research community.
 - For NHP species that are involved in research less frequently, their participation in research would require the development of adequate breeding colonies.
 - The feasibility of maintaining larger colonies of female NHPs for assisted reproductive efforts needs to be investigated.
 - Mechanisms need to be developed to support the maintenance and expansion of new models of human disease as they are produced.
 - The Caribbean Primate Research Center in Puerto Rico might be underutilized. This facility is a good source of Indian-origin SPF rhesus macaques and enhancing access to animals and facilities should be explored.
 - NIAID is collaborating with Alpha Genesis, which maintains a breeding colony to meet the needs of the research community. Other ICOs might form similar collaborations with commercial entities to support research specific to their Institute missions.

Open Discussion

Attendees were requested to discuss the following issues:

- The need to increase the capacity of NHP colonies and animal availability and renovate the infrastructure of the existing NHP resources, including NPRCs.
- The need to adapt funding to new NHP-focused scientific objectives, such as by rebalancing P51 funding to support the NPRCs and address the shortfalls and mismatch of funding through R01 mechanisms. To address these needs in the context of the constraints and demands of new SABV policies, rigor/reproducibility, and study power; and in terms of funding mechanisms such as the R21 and how they might be adapted to the needs to support discovery and high-risk R21-like exploratory projects in the context of realistic budgets.
- Reviewers' familiarity with NHP work, demands, and preclinical and translational value.
- The need to strengthen the existing infrastructure and support new-model development, particularly related to:
 - Marmosets as a more practical and grant-friendly model of NHP work, as well as their applicability to studies of social, communication, behavioral, and cognitive questions
 - Mauritian cynomolgus macaque breeding
 - Whole-genome sequencing and advancing the development of well-annotated genomes, which will be essential to maximize the value of existing colonies and enable somatic genomic editing *in vivo*
- The need for individual ICOs to dedicate funding and strategic planning to support the NHP portfolio, as shown by HIV research conducted through OAR and NIAID.
- The need to secure the supply of NHPs from international sources in light of political considerations

In discussion, the following points were made:

- Current resources must be assessed to make progress on these issues. Once resources are assessed, efficiencies can be developed that will maximize the capacity of existing resources and illustrate which resources must be expanded to meet the need.
- Attendees discussed the geopolitical pressures associated with the import of Chinese NHPs, agreeing that domestic breeding programs must be developed, despite the allure of low-cost imports, to prepare for the future.
- Participants noted that, although Japan has significantly invested in a top-down marmoset system, the colony at Johns Hopkins University shows that a distributed marmoset system is possible. The United States' extensive university structure may be able to support such a system for marmosets with more flexibility than for rhesus macaques, and a centralized marmoset production center at one or more of the NPRCs may help facilitate distributed use. Local marmoset colonies would allow researchers to have their animals nearby, and marmosets are relatively straightforward to maintain and breed in a conventional setting with the appropriate expertise.
- Attendees commented on the lack of standardization in marmoset care and suggested improving evidence-based decision-making and agreeing to unified standard operating procedures. Marmosets are susceptible to stress-induced gastro-intestinal disruption and will need to be transported, particularly if transgenic marmoset development is successful. Standardization will make studies conducted at different locations comparable. Attendees emphasized that it is prudent to plan ahead for maintenance of transgenic NHPs rather than waiting until after they are successfully developed.
- A participant commented that market increases in the cost of NHPs are limiting and questioned how NHPs could be provided at prices closer to the actual cost. NPRCs are limited by budgets and must recover the costs of raising and shipping animals, but commercial production often varies in quality. Additionally, NIH supplementation of costs allows investigators to pay a fraction of production costs at NIH-supported institutions, which may be a deciding factor in whether investigators can afford to acquire animals.
- NIH support in the early stages of establishing domestic marmoset breeding systems will be required; after many laboratories are supporting marmosets, the private sector could create a successful business model. Attendees discussed whether NIH's partnership with Alpha Genesis could serve as a model, but some participants were skeptical about commercial entities' stability and longevity. Participants also discussed how to leverage the different strengths of both business and science groups and noted that other animal model support structures, such as mice and swine, may not apply to NHPs because of differences in cost and existing infrastructure, such as that for the pork industry.
- Attendees questioned whether other aspects of NHP use, such as ART/IVF embryo transfer, or other species could be centralized.
- A participant commented on neuroscience-related urgency in supporting marmoset models, noting that the purpose of models is to distribute them to anyone who wants to use them, but resources are required to support them as they mature. Another participant pointed to this issue as an example of the need to centralize marmoset production.
- An attendee commented that the only NHP species that has become self-supporting is the rhesus macaque, which is related to the high price that resulted from HIV/AIDS research needs. The private sector might bid for contracts if the NIH could project future use for several years, but that often is not possible.
- Attendees discussed how to engage ICOs to dedicate portions of their budgets to NHP research and thus better serve their constituents. A unified effort to encourage NHP researchers to respond to RFAs could prepare researchers to take advantage of funds that become available. If researchers monitor concepts that have been approved but not yet moved to RFAs, a lead time of several months would be available to prepare a successful application.

- A participant noted that program project grants are rarely used but provide an opportunity to create fruitful discussions and partnerships across ICOs. A trans-NIH resources committee could help further additional cross-Institute efforts.

Day 1 Closing Remarks and Adjournment **Stephanie Murphy**

Dr. Murphy noted that the morning's presentations had examined program priorities and their impacts on NHP needs and demands, and the afternoon sessions had focused on the scientific factors that affect NHP needs and demands. The Day 2 agenda would focus on supply.

Important discussion points noted throughout Day 1 included the following:

- **Challenges in predicting and communicating NHP needs.** Some discussants felt that available funding drove some of the predictions. PI-initiated research and the peer review process are important in informing and predicting needs. Needs and demands from the level of the investigator, the supplier, the resources, and the funding agencies were discussed. Forum attendees discussed the needs as well as strategies for addressing these needs, but prioritization of these strategies is required. Improved access to information, particularly the need for better data collection and data sharing, was also discussed.
- **The need for better reporting and data collection/sharing.** The field needs to improve tracking NHP use overall, by species and by other factors (e.g., age, sex, reproductive/genetic/phenotypic status), and to track this use at the investigator, research area, NHP center/resource, funding agency, and ICO levels. The need for unique identifiers to track individual animals and link them with their associated data was noted; this would fit into the research resource identification movement. Forum participants noted the need for a trans-NIH working group to promote information within the NIH, as well as meetings to promote access to information needed both within and outside of the NIH. Discussion also focused on how the NIH might be able to adjust some of its databases to facilitate tracking NHPs. The concept of researcher consortia was discussed from the perspective of improving the community's understanding regarding the existing resources and networks for different species and research areas. Additionally, the need for a primate census was noted several times, as was creating resource directories or summaries to help inform the community, reduce overlapping efforts, and enable the field to more effectively use available resources.
- **Strategic planning processes.** There was significant discussion on strategic planning processes at the NIH level, at the ICO level, and at the level of the institutions that host NHP resources. One caveat noted was that strategic planning processes often focus on scientific priorities and not necessarily on resource priorities.
- **Planning new initiatives and programs.** Early in the day, Dr. Hild provided several examples of how ICOs planned effective programs and initiatives. Critical to these efforts is careful consideration of the components needed to support these programs and initiatives, including resources.
- **Challenges associated with the resource planning process.** The challenges include new resources, maintenance of current resources, and expansion of current resources. Forum participants mentioned infrastructure limitations, and the issues of scientific rigor and reproducibility were noted several times. Questions related to this topic were discussed including:
 - What are the appropriate mechanisms for supporting new or maintaining or expanding these resources?
 - Should there be disease-specific or shared resources?

There was additional discussion on outreach efforts related to the value of NHP models within the context of available and future resources.

- **How will NHP needs progress moving forward?** Forum participants discussed centralized, shared resources versus individual-driven resources, the different models that are currently available, and how to meet the different types of needs. Community opportunities were mentioned in the context of pooling existing resources, multi-PI proposals, and co-funded proposals. Scientific factors were also discussed—many emerging technologies and tools were mentioned (e.g., gene editing, imaging).
- **Infrastructure.** Key considerations in this regard include maintenance and expansion.
- **Rethinking what NHP resources should or could be.** Questions addressed in this area included: Are NHP resources simply a source of animals? Services, technical expertise, training, and research data-sharing considerations were discussed at several points throughout the day. Are there other things the field should be thinking about to make these resources more efficient or more attractive?
- **Compatibility of research using NHP models with the current NIH grant cycle and available mechanisms.** This topic was discussed on several occasions. The example of trying to coordinate one's grant submission process with the NHP breeding seasons was highlighted. Some mechanisms support resources; for others, it is extremely difficult because of the type of model being used.
- **Focus on cross-cutting issues.** Specifically, forum participants suggested a focus across research disciplines as well as specific diseases.
- **Model(s) selection.** Participants discussed whether more investment is needed in established models. They also discussed how to prioritize so that new model development and model evolution can occur.
- **Development of cellular/molecular/other tools, reagents, and technology.** At several times during the forum, attendees expressed the need to prioritize and expand the reagents for other species.

Forum Day 2

Session 3: Factors Impacting on Supply of NHPs for NIH-Sponsored Research

Session Co-Chairs: Chris Abee and Skip Bohm

Chris Abee opened the second day of the forum with a reflection on the past and changes that have occurred. Lower costs and higher supply of NHPs made NHP research relatively easy in the past, in contrast to the situation today. This meeting could affect possible futures for NHP research, which include access, rather than merit, determining what research is conducted in the US or NHP research leadership shifting overseas. Dr. Abee suggested that this group needs to look for a future in which this country can maintain leadership in biomedical research, specifically with NHPs, and that necessary research can be conducted at reasonable time and costs.

Use of NHP Studies for Decision Making in Viral Vaccine Development at Pfizer

Phillip Dormitzer

Phillip Dormitzer explained that all human vaccines developed at Pfizer are first tested with NHPs and described the NHP tests for a respiratory syncytial virus (RSV) vaccine and a CMV vaccine. The RSV vaccine candidate, when tested in rhesus macaques, showed successful transmission of immunity through the placenta and justified a confident investment in a large human trial. A CMV vaccine candidate that elicited neutralizing antibody titers similar to natural CMV infection was tested in a horizontal transmission model (primary infection after oral challenge) in CMV-negative NHPs. The vaccine elicited strong antigen-specific cell-mediated immunity but failed to prevent infection following oral challenges. This resulted in an immediate disinvestment in the program; Pfizer considered this a large waste in resources and this may have been the case. However, additional studies performed in collaboration with

Sallie Permar, suggest the Pfizer vaccine candidate might have potential to block vertical transmission of CMV (mother to fetus transmission through the placenta). The critical study to evaluate the vaccine for efficacy in preventing congenital CMV could not be completed due to the lack of available CMV-negative female rhesus monkeys. Thus, it is not clear if Pfizer abandoned a viable vaccine for a crucial disease or prevented costly fruitless human trials.

Expert Panel Discussion

Panel Members: Boris Predovich, Jay Kaplan, Suzette Tardif, Robert Adams, Robert Norgren, Phillip Dormitzer, Alphonse Cisar

Skip Bohm explained that the panel met previously by teleconference to discuss the objectives and commented on the way previous day's discussions had also addressed each objective for this session.

- *What are the expectations for continued future supply of imported NHPs from China or other countries, and what (if any) effects are expected on industry and the competition between industry and academia for supplies of domestic NHPs?* Dr. Bohm noted that the previous day included discussion of what China is doing with regard to biomedical research, potential outcomes if China cuts the supply of NHP imports, and how such a reduction would affect NIH resources if industry is competing directly for the same resources. The outcome of these trends will likely have a negative impact on NHP research in the US, particularly for NIH investigators.
- *Should existing colonies be expanded, or other additional domestic colonies be established to augment commercial sources, and what additions are suggested for increasing the value/impact of existing colonies?* Previous discussions touched on quality, characterization, deep pedigrees, large investments already made in colonies, the decision to expand existing colonies or create new colonies, and potential partnerships with industry to expand or create colonies.
- *Aside from simply increasing production, are there other actions that NIH-sponsored NHP centers can take to make animals more accessible to grantees (e.g., increasing external sales)?* Dr. Bohm noted that the previous day's discussions included generalizations about what NPRCs or other NHP resources can provide and the difficulties some researchers outside these resources have experienced when trying to access animals. Dr. Bohm emphasized that this difficulty should not be a universal assumption and encouraged attendees to discuss how to facilitate informing researchers about available animals.
- *Should animals from NIH-sponsored NHP colonies be made more accessible to not-for-profit and industrial users?* Dr. Bohm referred to Dr. Dormitzer's presentation and the NIH priority of allocation outlined previously and asked attendees to consider whether that prioritization scheme should be reexamined.
- *How can NIH ICs contribute information to improve the forecast and planning process for future NHP needs?* The previous day's discussions illustrated wide agreement on the difficulty of gathering necessary data on this issue and included potential solutions to capture those data.

Dr. Bohm introduced the expert panel members, and each provided short remarks prior to open discussion.

Chris Abee

Dr. Abee gave an overview of the NHP populations at the Keeling Center for Comparative Medicine and Research, including SPF baboons, owl monkeys, rhesus macaques, and squirrel monkeys. The baboon resource is funded by an NIH P40 grant. The baboons are free of all indigenous viruses and are useful in xenotransplantation research. The owl monkey resource is self-supporting through sales and provision of research services using these animals. Owl monkeys are used in malaria and viral research. The rhesus macaque resource also is self-supporting. The squirrel monkey resource is the only national research resource of this species and is funded by an NIH P40 grant. Squirrel monkeys are used in malaria research and neurology research. The self-supporting owl monkey and rhesus macaque resources provide animals to industry and academia. The baboon and squirrel monkey resources give priority to NIH grantees and the NIH Intramural Research Program.

A participant asked whether the owl monkey resource could be free-standing without the supporting infrastructure of the other resources. Dr. Abee replied that the only animals that could sustain a stand-alone resource are Indian-origin rhesus macaques; other resources need to be subsidized. One way to support a colony would be to raise the price of the animals. However, if the prices are too high, researchers may not be able to afford them. Even if income was adequate during periods of high demand, resources would not be sustainable during periods when demand drops.

A participant noted that, in anticipation of times of high or low demand, researchers have discussed maintaining a “strategic monkey reserve.” Support must continue in times of low demand. Production could increase dramatically by putting non-vasectomized males with females. However, the offspring would not be available for research for 3 to 4 years. One way to meet spikes in demand is to have a population that is high but steady.

A participant noted that the NIH pays in either case. If prices are raised to sustain a colony, the NIH pays for the animals through research grants. If the NIH gives more money directly to the resource to drive prices down, the NIH is still paying. More researchers might submit grants if NHPs were cheap enough to support with R01 grants, and this would also lead to more NHP research. Attendees suggested that providing a subsidy directly to a resource works better to sustain a breeding colony than waiting for money from grantees. Dr. Abee pointed to the importance of a mechanism to support the resource in terms of weathering demand fluctuations. NIH-supported NHP Centers, including the NPRCs, have complex obligations as they are expected to meet the “National Need”, which is not well-defined, and to use a prioritization scheme based on project funding support (e.g., NIH, Federal agency, not-for profit, or for-profit); this makes it difficult to plan for changes in supply and demand.

Boris Predovich

Boris Predovich offered some observations about commercial suppliers of NHPs. A number of commercial suppliers no longer sell animals but instead offer them for research at the supplier’s research center. Animals kept in the supplier’s research center can be worth \$50,000–\$60,000. Mr. Predovich predicted that China will become a leader in primate research, although he noted that this does not mean that China will be taking research away from the United States. He suggested that industry collaborations can be an asset to nonprofit research organizations.

In response to a question about China’s breeding capacity, Mr. Predovich commented on recent improvements in Chinese breeding programs. He also recommended that U.S. Government agencies interact more collaboratively with industry, taking advantage of industry’s ability to create new resources rapidly if they are allowed to be profitable.

Jay Kaplan

Jay Kaplan offered a historical perspective on NHP research, describing a 1986 collaboration between several U.S. NPRCs and a university in Indonesia resulting in the import of 15,000 cynomolgus macaques. He also commented on Wake Forest University’s African green monkey resource, which is the only NIH-supported center for this species. Dr. Kaplan noted that the P40 grant for this resource is capped at a much lower level than the costs required. African green monkeys are good models for a range of diseases, including type 2 diabetes, Alzheimer’s disease, and heart failure, and have been used in aging research and infectious disease vaccine development. Dr. Kaplan noted that African green monkeys are models for the majority of diseases that comprise the United States’ public health burden.

Dr. Kaplan agreed that a better understanding of resource availability is needed and called for the creation of a national NHP consortium. In response to Mr. Predovich’s comments, he noted that although industry sometimes is reluctant to make the long-term commitment required to fund the costs not supported by Wake Forest’s P40 grant, collaboration between researchers and industry is required to sustain the colony at the size needed to address important public health needs.

A participant suggested more detailed assessment of the difference between industry and NIH business models.

Suzette Tardif

Suzette Tardif described the effects of the pressing demand for marmosets on the Southwest National Primate Research Center (SNPRC). The queue for the center's marmosets is about 180–200 animals; the center's present population is approximately 330 marmosets. The planned collaboration with the University of Texas-Health's Barshop Institute for Longevity & Aging Studies is expected to expand the population to approximately 400 animals by the beginning of 2019, with that increase already committed to funded projects through NIH-NIA. Of the present SNPRC population, about 22% is devoted to breeding, 35% are infants or juveniles, and 8% are geriatric, leaving approximately 110 adult animals. Of those, approximately 60 are committed to on-going projects at SNPRC, including nutrition and obesity studies, Zika pregnancy studies, and aging studies requiring young control groups, leaving around 50 animals that can be used for new projects, replacement breeding and sales. Based on this the SNPRC expects to sell between 10-30 animals per year over the next few years. Finer-grained information about requests, such as type of studies, location, and timeline of need, would be useful to formulate a production needs forecast. Dr. Tardif noted that successful transgenic models will require the center to expand its capacity to characterize and develop those lines. She noted that large commercial production entities could be engaged to help meet marmoset demand, as entities producing rodents are likely to have facilities easily modified to suit marmosets, but commercial producers should have a demonstrated expertise in the species. Establishing a community of investigators and support staff, such as veterinarians and colony managers, could work toward evidence-based standardization of marmoset management. Part of standardization is sharing information about and learning from failures. A community of investigators also would be useful in establishing genetic management plans for small breeding marmoset populations, something akin to zoos' species survival plan.

A participant remarked that marmosets are better suited to university-based breeding than large monkeys. He suggested increasing marmoset populations in these settings with additional NIH funding to supply the animals to local and regional investigators. In answer to a question, Dr. Tardif said that almost all investigators want marmosets to start their own breeding colonies rather than to use them immediately in experiments. The center's priority for distributing its marmosets is to NIH-funded programs.

Robert Adams

Robert Adams discussed the factors impacting the supply of NHPs for NIH-supported research. He provided a historical overview of the NHP facility at Johns Hopkins University School of Medicine. Since the 1970s, wild-caught rhesus macaques were housed at this facility because of the scarcity of research animals. This facility houses a variety of NHPs, such as pig-tailed or rhesus macaques and marmosets. All the currently housed animals are derived from wild-caught breeders and are commercially available. The rhesus macaques are used mainly for long-term studies (e.g., neuroscience). Researchers at the School of Medicine are using the simian immunodeficiency virus (SIV) model in pig-tailed macaques because these animals develop central nervous system (CNS) disease that greatly mirrors HIV-associated CNS ailments in humans. Further demonstrating the usefulness of these animals, Dr. Adams mentioned that he and his collaborators discovered a genetic susceptibility marker for CNS disease. While continuing to grow the colony, about 50 percent of pig-tailed macaque male offspring have been sold to NIH researchers studying primarily AIDS. Dr. Adams indicated that animals are housed indoors and outdoors. The facility lacks funding for expansion, which would entail the construction of a large open field for the animals. To increase NHP accessibility to grantees, he proposed that the animal locator be provided to the NHP research community. He emphasized the need to identify a source for breeders when establishing a new colony.

A participant remarked that researchers must be more judicious regarding the use of their animals and should perform more minimally invasive procedures.

Robert Norgren

Robert Norgren addressed the genetic approaches to increasing the utility of NHP models. More funding is needed to support animal models (i.e., NHPs) that are more biologically relevant to the human than mice. Genetic editing modalities, such as CRISPR-Cas9, exist to develop novel animal models; however,

lower cost approaches should be evaluated. Dr. Norgren noted that genome sequencing was used to develop more than 50 different NHP models of human disease, reproduction, and immunology. Dr. Norgren's laboratory identified naturally occurring heterozygote mutations in NHPs that are linked with human disease. Genetic screening via sequencing has identified variants that also are found in humans and can be used to breed heterozygotes and generate homozygotes. Increased efficiency, high-quality assemblies and annotations, and the use of a reference genome are necessary to eliminate false positives and avoid unnecessary costs. The cost of human trials far exceeds that of studying NHPs, and changing how funding is allocated will improve access to NHP models.

A participant commented that many researchers use mice because these animals are more readily available and genetically characterized.

Alphie Cisar

Alphie Cisar described the availability of U.S. government-funded NHPs. He commented on the need to reduce U.S. laboratories' reliance on China for the importation of NHPs. Identifying domestic sources is necessary to maintain the high standard of biomedical science and respond to emerging diseases, and existing U.S. NHP colonies should be expanded. Mr. Cisar recommended that commercial, pharmaceutical, and government entities create a plan of action regarding the use of domestic sources and remarked that the NIH does not have a long-term solution for the availability of NHPs.

Assessing trends regarding the supply and demand of NHPs and consolidating resources across the U.S. government will be important. Engaging representatives from the Biomedical Advanced Research and Development Authority, along with establishing annual NHP meetings, would be beneficial.

In response to a question from a participant, Mr. Cisar expressed support for proper management and better experimental forecasting as methods required to meet the needs of the NHP programs. Improved communication among all NHP stakeholders also is needed.

Phillip Dormitzer

Phillip Dormitzer wondered if the pharmaceutical industry, as a major user of NHPs, could be part of the solution to supply problems by absorbing or mitigating fluctuations in supply and demand caused by variable NIH funding. He commented that the pharmaceutical industry conducts both its own research and studies in collaboration with other parties. When innovative science is needed, collaborations with academics or the U.S. government are sought, but more service-oriented or high-quality studies are done in collaboration with commercial or private groups, which often have more capacity to employ extensive quality control standards at a lower cost. Dr. Dormitzer wondered if some routine tasks currently executed at NPRCs could be designated to commercial groups, leaving NPRCs to fulfill their role as premiere scientific centers. Dr. Dormitzer also commented on funding provided for studies known to be ineffective, such as flu studies in the mouse, which could be more appropriately done in a different animal model. Better access could provide opportunities to improve the quality of work. Dr. Dormitzer noted that an important concern when considering Chinese biomedical research is the advantage of the United States' intellectual property (IP) laws.

Session 3: Open Discussion

In discussion, the following points were made:

- Attendees noted that partnerships with industry would require strict standards of practice to ensure the necessary quality, adding that research institutions often have the ability to do more costly studies that advance the science.
- An attendee clarified that a temporary shortage of NHPs is not a failure of the NPRC program but a positive growing pain reflective of the program's success; such shortages could be mitigated by temporary gap-filling funding measures. A commenter clarified that these shortages are not

perceived as a failure of the NPRCs as much as an illustration that they cannot meet all of the need.

- Attendees commented that collaborations with commercial researchers are complicated by NIH preferences for which commercial centers are used, which is not fair from an IP point of view.
- Regarding biomedical research in China, attendees noted that previous studies have been published that turned out to be inaccurate and China does not have the same track record of outstanding science as institutions in the United States.
- A commenter pointed out that there is no cross-colony, national program for whole-genome sequencing, which should be performed for every Indian rhesus and marmoset born to all colonies in the United States. The lack of these data mean that current colonies are massively under-utilized, but it provides the opportunity to maximize the value of the existing colonies. Whole-genome sequencing could allow studies of genotype-to-phenotype transitions and phenotype-to-genotype transitions. A national NHP program or commission with the appropriate bioinformatics support will be necessary to gather these data and make them shareable. NPRCs now have the information technology infrastructure to share these types of data and provide researchers with more information about each monkey.
- An attendee commented on the need to know each animal's rearing and social conditions for behavioral research, which limits the ability to source animals from multiple groups.
- Transportation issues were discussed. The East or Northeast section of the United States does not have a local NPRC, and flying restrictions make it difficult to get NHPs. Internationally, some airlines are willing to transport NHPs, but others are not, so there are gaps in the transportation chain, and it can be difficult to negotiate this delicate subject. Government regulations may differ between countries. For ground shipping, rides also can be shared to reduce costs.
- Availability is also an issue in whole-genome sequencing. Researchers may request animals that have been sequenced, but may need to pay the per diem costs while the sequencing is conducted because these animals cannot then be distributed to the next person on the waiting list. Some of these redundancies could be assuaged by better data sharing.
- If whole-genome sequencing becomes a standard test for research NHPs, that genotype could become part of each individual's health record, which would narrow some of the repeated unnecessary expenses.
- Sequencing is necessary to discover genetic variability, but once that variability has been sampled, subsets of other items to look for in the populations could be defined. A standard chip could be developed that is the same for each individual in a species based on characteristics that investigators agree are important, and this chip could be used to genotype each animal and determine which to breed. The most difficult aspect of this process is the bioinformatics piece; relatively few institutions have the capacity to conduct bioinformatics on that level.

Attendees were asked to provide specific recommendations or suggestions, as well as succinct comments, about items to prioritize or revisit. Moderators emphasized the importance of the need and the agreement among attendees that the need is greater than the supply. Additionally, attendees had noted that geopolitical threats could impact the availability of resources, so attendees were encouraged to think about domestic resources and how to meet critical needs domestically.

- Attendees recommended that the NIH take a lead on facilitating communication between groups.
- A participant suggested that, although work in rodents is irrelevant in some fields, it continues to receive funding; these resources could be shifted to NHP research.
- Participants agreed that international imports are not a sufficient long-term plan and the expansion of domestic colonies is necessary to sustain U.S. NHP research. The interim steps, especially regarding cynomolgus macaques, must be determined. This may require a trans-NIH stakeholder summit to review all resources and determine how to expand.

- Maternal/fetal studies in NHPs are critically needed because NHPs have the only placental and immunologic interface that mimics that of humans. Attendees suggested that fields that specifically need NHPs be prioritized. Another example is the need for herpes virus-free colonies, the lack of which limits the development of a vaccine for CMV, the largest worldwide contributor to birth defects. Other participants cautioned against plans to exclude pathogens from entire colonies, which could have unintended consequences and restrict possible models available for different studies.
- An attendee suggested that study sections are more likely to make specific funding decisions than the NIH as a whole. The specific needs for NHP research should be identified and described in a way that provides study sections, which may not include many researchers familiar with NHPs, with a clear rationale for meeting those needs. Another participant commented on the lack of understanding of NHP issues on study sections and encouraged attendees who are asked to sit on a study section to utilize their NHP experience in the consideration of applications.
- A participant encouraged the NIH to provide resources to start and maintain Mauritian-origin and non-Mauritian cynomolgus macaque breeding programs in the United States with the conditions these animals require. Inexpensive cynomolgus macaques from China make starting a U.S. colony not financially viable, but domestic breeding is necessary to plan for uncertain international futures, and only an NIH-like entity could support such a program. Attendees agreed that the need to domestically breed cynomolgus macaques is essential and could jeopardize biomedical research in the United States as a whole if not met. They emphasized that it may already be too late to address this need but will certainly be too late within a few months.
- Dr. Murphy asked participants to discuss how to prioritize the identified needs, gaps, and solutions. She noted that this is the first effort at discussing this problem and the NIH needs guidance on which issues are more or less pressing; a subset of this group may need to reconvene to fully address prioritizing.
- Attendees emphasized that the increasing demand for marmosets must be attended in a way that meets the needs of this special animal, possibly by taking advantage of the capacity and willingness of many institutions to start supporting their own marmoset colonies.
- The highest-priority needs identified—domestic-origin cynomolgus macaques, marmoset colony expansion, and development of herpes-free rhesus macaque colonies—will likely require a follow-on meeting to suggest adequate approaches. The NIH requires that researchers create a strong rationale for meeting such needs, and the NIH will then develop a mechanism to meet that need.
- Attendees noted that sequencing and genotyping, toward which the field is already trending, will make existing and future domestic resources more valuable. A participant recommended that researchers consider whether a “Chinese cynomolgus macaque” is fundamentally different from a cynomolgus macaque from Cambodia or Vietnam; genetically, these animals are very much the same, and the community could agree that they are the same animal, which would immediately reduce the risk associated with unstable Chinese exports. If a domestic program is developed to meet the need for cynomolgus macaques, researchers have the opportunity to determine what is considered the standard cynomolgus. This would require sequencing and genetic characterization up front, agreeing upon desired qualities, and then starting the U.S. colony.
- Participants recommended recruiting researchers who are knowledgeable about the sourcing of cynomolgus macaques and how to seed colonies; existing cynomolgus macaques may have significant variability due to their nature as an island species.
- Participants suggested that follow-up meetings could gather a core group of PIs working with each species; for example, a core group of PIs who represent the cynomolgus macaque research community, particularly NIH-supported research, could put weight behind the value of the model and therefore the value of the resource.
- Attendees discussed potential vehicles for creating a model, such as a national genotyping resource or funding a smaller operation in multiple sites. A large center could be funded to conduct the sequencing and ensure that the appropriate reference genome is available to align against, and several specialized groups could conduct variant analysis on the reference genomes

for different species. Participants emphasized that the “recipe” created can be followed at multiple locations but will determine the “genetics road” that is followed.

- Attendees agreed that the NIH could support this process by forming a consortium to organize tasks and ensure that researchers at every location are fully informed. Similar resources were created at DCM/ORIP for *Drosophila* and zebrafish and could serve as a model.

Closing Remarks/Highlights

Stephanie Murphy

Dr. Murphy briefly summarized the discussions and issues surrounding NHP supply. She noted that in the past, animal availability and cost were not the limiting issues. Current issues include limited animal and infrastructure availability, increasing costs, need outstripping supply, and geopolitical threats. Finally, the future will focus on the potential shift of NHP research outside the United States.

Important discussion points highlighted during the closing remarks included the following:

Impact of NHP availability on product development. There were some real-world examples from various Day 1 discussions about the impact of NHP availability on product development. Attendees discussed the need for a cost analysis to determine the most cost-effective strategies to balance supply and demand. The focus needs to switch from numbers to cost. Attendees also talked about the different mechanisms the NIH uses to support NHP research, including research project grants, which are more direct, individual resources, versus resource grants, which are a top-down approach allowing for some subsidy.

Better communication and forecasting on supply and demand among stakeholders. Attendees identified the need for better communication about NHP needs in general, and about forecasting and supply and demand among stakeholders in the context of PIs, suppliers, resources, ICOs, and other funding agencies. Accessibility of the data on animal availability, along with a resource directory, and the concept of an animal locator database all were topics of discussion.

Attendees discussed a primate summit or other meetings as vehicles for keeping these NHP conversations going. They also identified the need for trans-agency discussions to share ideas and pool resources, not just within the NIH but also within other departments and agencies. The need for data sharing has been raised repeatedly, along with the need to prioritize needs, gaps, and strategies that attendees identified.

Best model for research. Attendees discussed the need to start thinking about the best model(s) to address the scientific questions. The focus should be on the best model for the research based on the science, rather than availability, funding, or other driving factors. The science should be driving the funding, rather than funding driving the science. Attendees discussed NIH collaborations with commercial suppliers, industry, and other private enterprises. An important distinction was made among the perspectives of those groups about selling the monkey versus selling the monkey study.

Business models. Attendees discussed the pros and cons of various business models. For example, industry can take a short-term view, can build infrastructure quickly, can provide support, and is profit-driven. The NIH can take both short- and long-term views but has limitations based on regulations and appropriations.

National consortium. Attendees discussed the idea of a national NHP consortium, including NHP working groups focused on different topics. Along with that was a discussion of a community of PIs and support staff to:

- Share expertise, successes, and failures
- Discuss standardization and best practices across NHP species
- Share data

Critical mass determination. Attendees discussed the need to determine what critical mass must be sustained to protect IP, fulfill current research needs, and respond to emerging health needs, as well as how domestic resources can meet these critical needs.

Future production needs forecasts. To forecast future production needs, the type of use must be taken into consideration. For instance, do researchers need aging or pregnant animals? Will animals be used for transgenic applications? Will the studies be invasive or noninvasive? A strategic monkey reserve is needed to address fluctuating demand and reduce production lags when demand does increase. Attendees also mentioned genetic management plans, a genotyping consortium, and maximizing existing colonies by:

- Increasing the animal supply
- Using (and reusing) animals more judiciously
- Using phenotype-to-genotype processes to enhance animal assignment (bioinformatics, genome sequencing components to make this possible)

Importation challenges. Issues related to importation challenges included:

- Transportation by air and ground
- Available routes
- Animal screening
- Data sharing

In response to a question, Dr. Murphy clarified that funding and appropriations are a limitation, but decisions related to these questions would need to be made at a trans-NIH level.

Adjournment

Forum leaders thanked all participants for contributing to stimulating and enlightening discussions and requested that they continue to contribute to future discussions and activities. Participants were commended for raising important questions about how to prepare for the future and take advantage of technology investments to improve the use of NHPs as models for human disease.