

**National Cancer Institute  
Needs Assessment of the Mouse Models of  
Human Cancer Consortium**

***Stakeholder Satisfaction Telephone Survey  
Final Report***

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## EXECUTIVE SUMMARY

Mouse and human-in-mouse models are used in basic, translational, clinical, population, and pharmaceutical research. Recent advances in the development and popularity of mouse models as tools for personalized cancer treatment are reflected on the cover of the October 3, 2014, issue of *Science*, which also contains articles about “The Littlest Patient” and “Hope in a Mouse.” The quality of the research using mouse models depends on the availability and appropriate selection of models, the reliability of the data that are generated from the animals, and guidance on best practices that ensure robust experimentation in mouse models. As research using mouse models has expanded, concerns have been raised about the reliability and robustness of the models and about how well the resulting experimental data inform research that is designed to benefit patients directly. To address these issues, The Scientific Consulting Group, Inc. (SCG) provided support to the National Cancer Institute (NCI) to conduct a comprehensive assessment of the needs of the cancer research community for a widely deployed suite of cancer models to support basic research and translational applications. The first part of the assessment—documented in this report—was accomplished through a stakeholder satisfaction telephone survey instrument that probed for information about the needs of 100 NCI stakeholders who benefit or could benefit from using mouse models.

In collaboration with the NCI, SCG identified basic, clinical, translational, and epidemiological researchers in academia, as well as researchers from the private sector, who currently use, or could use, mouse models. Potential interviewees were sent an email invitation, and those who agreed to participate provided informed consent. Telephone interviews were conducted, and the responses were analyzed for key themes. Common themes emerged from all of the stakeholder groups. Indeed, interview responses were more alike than different across groups. In this report, stakeholder input is classified into five general categories: the *Research Questions and Emerging Opportunities* category includes specific topics that scientists mentioned as warranting additional research in the categories of translational research and drug discovery. The *Mouse Model Improvement* category comprises suggested priorities for developing models that more accurately represent human disease. *Cancer Research Community Resources* includes themes related to research and institutional capacity that should be augmented within the cancer research community. The *Development of Tools and Techniques* category is composed of specific methods and practices that should be pursued to facilitate translational mouse research. The *Collaborations* category includes high-priority partnerships that should be fostered to advance the field.

Following all of the interviews, responses were coded according to mention of 36 specific keywords and phrases distributed across the five categories. The 100 cancer research community stakeholders interviewed identified the following as their top 10 priorities:

- Improving communication and collaboration between researchers.
- Supporting private-academic partnerships.
- Characterizing and validating mouse models.
- Developing a mouse model database.
- Increasing funding for mouse model research.
- Focusing on genetics and genomics.
- Increasing awareness of the importance of mouse model research.
- Standardizing methods and analysis.
- Building humanized mice.
- Developing improved PDX models.

The next phase of the assessment involves focus group discussions for the five stakeholder groups to further explore high-priority needs for the use of mouse models within the cancer research community.

## INTRODUCTION

The Scientific Consulting Group, Inc. (SCG) provided support to the National Cancer Institute (NCI) Division of Cancer Biology (DCB) in conducting a comprehensive assessment of the needs of the cancer research community for a widely deployed suite of cancer models to support basic research and translational applications.

The NCI's Mouse Models of Human Cancers Consortium (NCI-MMHCC) was established in 1999 to capitalize on technologic advances in human cancer modeling by altering genes of laboratory mice. After more than a decade of success, the program identified a number of new research and applications directions that would not be accommodated by simply changing some aspects of the NCI-MMHCC. In 2014, the NCI-MMHCC program will end, and the NCI is currently striving to create an international program to define, assemble, and deploy best practices for applying faithful cancer models as translational research tools. DCB wanted to explore establishing a new program that would evolve and maintain an open Oncology Models Forum that addresses mouse model issues for all cancer research communities. In-depth interviews were planned to inform how the NCI could formulate a new program and deliver services, resources, educational products, and opportunities for cross-community collaborations (connecting mouse oncology modeling experts with members of other oncology communities). To achieve its mission, the NCI requested contractor support to conduct the communitywide needs assessment to help ensure that opportunities that may arise as a result of connections to, and collaborations with, other ongoing efforts and existing infrastructure are not missed.

Mouse and human-in-mouse models—such as genetically engineered mouse models (GEMM), allograft or xenograft transplantation models, and patient-derived xenograft models (PDX)—are used in basic, translational, clinical, population, and pharmaceutical research. The quality of the research using mouse models depends on the reliability of the data that are generated from the animals, the appropriate selection of models used, and guidance on best practices that ensure robust experimentation in mouse models. The purpose of the assessment was to better understand the information and research needs of the scientific community that benefits or could benefit from using mouse models. The assessment relied on conversations with basic, clinical, translational, and epidemiological researchers from both academia and the private sector to provide insights on the following:

- How the cancer research community develops and uses mouse models.
- Types of research that would benefit from the application of mouse models.
- Emerging opportunities and challenges related to the integration of mouse models in basic, translational, clinical, and epidemiological research.
- Training and educational needs of the research community to make best use of mouse models in basic, translational, clinical, and epidemiological research.
- Collaborations that would benefit the research community through the development of best practices in the use of mouse models.

Stakeholder input that was provided during the assessment interviews will be very important to the cancer research community, as the NCI will use the responses to determine: (a) the most important research questions to address using translational mouse models; (b) emerging opportunities or persistent challenges related to mouse model research; and (c) collaborative opportunities designed to leverage other relevant efforts at government, academic, nonprofit, or private sector institutions.

## METHODS

In collaboration with the NCI, SCG identified basic, clinical, translational, and epidemiological researchers in academia, as well as researchers from the private sector, who currently use, or could use, mouse models. The researchers were evaluated for mouse model expertise, cancer research experience, and field of study. A prioritized list of stakeholders was developed and submitted to the NCI to confirm selection of interviewees. Upon approval, potential interviewees were sent an email invitation that included an explanation of the importance of the interview. Stakeholders who agreed to participate in the interview were asked to read and sign an informed consent form and were provided with the interview questions for review. Telephone interviews were conducted, and the responses were analyzed for key themes and important issues for the cancer research community that the NCI needs to address. Each phase of this process is explained in further detail below.

### *Materials Preparation*

To prepare for the interviews and ensure that all of the correct questions were asked, SCG performed an extensive review of the literature to become familiar with the state of cancer research, cutting-edge research topics, and types of mouse model research. Using the information gathered in the literature search and following extensive discussions with the NCI, SCG developed the following materials:

- **Interview Questions:** Draft interview questions for the five stakeholder groups (academic basic, translational, clinical, epidemiological, and private sector researchers) were crafted to elicit the desired information concerning challenges and opportunities for the use of translational mouse models in cancer research.
- **Moderator’s Guide:** An interview guide was prepared to steer the moderators through each conversation.
- **Recording Template:** An interview-recording template was created to capture stakeholder comments and identify key points.
- **Consent Form:** A consent form was drafted to communicate the purpose, procedures, and risks and benefits of the stakeholder survey to potential interviewees.
- **Glossary:** SCG prepared a list of common scientific acronyms, genotypes, and other terminology to be used as a guide for the interview moderators. SCG also developed a list of potential interview questions.

All of the materials were reviewed and approved by the NCI.

### *OMB Clearance*

The planned number of stakeholder interviews (100) required OMB clearance in accordance with the Paperwork Reduction Act. SCG prepared and submitted an OMB package that detailed the purpose of the study, identified potential benefits to the cancer research community, described the proposed respondents and type of data collection, and verified that personally identifiable information would not be collected. Included in the OMB package was a copy of the Interview Guide (Appendix A), Invitation (Appendix B), and Consent Form (Appendix C). The materials were designed to pass the OMB “fast-track” clearance process.

The study, titled “Customer Feedback of the NCI-MMHCC Program,” fit under the scope of the NCI’s Generic Submission for Formative Research, Pretesting and Customer Satisfaction to “determine the level of customer satisfaction with products that help the NCI identify strategies for improving the accessibility of materials/programs, their user-friendliness, and their relevance to the needs of ... health care

professionals.” After a lengthy review, OMB approved the stakeholder satisfaction survey under OMB #0925-0046, with an expiration date of 05/31/2016.

### *Stakeholder Identification*

SCG identified key stakeholders who could provide important insights into how to improve and promote the use of mouse models and continue the evolution of standard practices for the use of mouse models in academic research—basic, translational, clinical, and epidemiological—as well as in private sector research. We searched for stakeholders who develop mouse models; use mouse models for transdisciplinary research; conduct basic research using other techniques and/or model organisms that would benefit from new, relevant mouse models; or study diseases for which improved mouse models are needed. Many of the stakeholders included current or previous NCI grantees who have experience with the Institute.

Having worked closely with many NCI grantees in the past, SCG used historical knowledge and records of relevant experts within academia and industry to assist in identifying individual stakeholders within each group. We also conducted a literature search, reviewed recent high-profile publications to identify experts in certain areas, and searched for contacts at private sector organizations. The NCI provided additional names of potential stakeholders for consideration. Intramural NIH researchers and current NCI-MMHCC members were omitted from the list, and international researchers were avoided. All potential stakeholders considered for interviews were entered into a spreadsheet to collect and evaluate demographic and research characteristics. The spreadsheet captured the selected stakeholders’ capabilities, expertise, and affiliation. Specific fields included Name, Degree, Title, Department, Affiliation, Stakeholder Group, Biography Website, Relevant Information, Email Address, and Telephone Number. Stakeholders were assigned to one of the five groups according to their research summary, department of faculty appointment, and NCI recommendations.

From the list of approximately 220 experts considered for interviews, SCG selected 20 representatives for each of five stakeholder groups: (1) academic basic, (2) academic translational, (3) academic clinical, and (4) academic epidemiological, and (5) private sector. The stakeholders were assigned to one of the five groups according to their work and research history. A gap analysis of the prioritized list of stakeholders was performed to ensure an adequate representation across demographic characteristics, subject expertise, career stage, and institutional affiliation. Any identified gaps were filled with stakeholders with the relevant expertise or other necessary characteristics.

After SCG determined which stakeholders to engage, a draft list of stakeholder selections, including each expert’s affiliation, scientific specialty and stakeholder group designation, was submitted for the NCI’s approval. The prioritized list was evaluated by NCI staff, who reviewed the suggested stakeholders to confirm that the individuals were appropriate for participation in interviews and/or focus groups.

### *Stakeholder Recruitment*

Following the NCI’s approval of the stakeholder selections on July 14, 2014, the 20 prioritized stakeholders in each group were contacted to arrange voluntary interviews to elicit expert recommendations for the use of translational mouse models. The invitation email (Appendix B) communicated the goals and purpose of the NCI’s stakeholder satisfaction survey, the technical or substantive issues involved in the structure of the interview, and the timing and schedule for the interviews to potential participants. Participation in the interview was voluntary.

A very low response rate to the invitation emails was immediately apparent. Follow-up emails were sent to all non-responders, and potential interviewees were contacted via telephone as well when a telephone number was available. Of the original 100 prioritized stakeholders, only 37 agreed to be interviewed after

receiving initial and, as necessary, follow-up requests. Several approaches were employed to ensure that 20 interviews were conducted in each of the five stakeholder groups. First, additional stakeholders from the original list of 220 experts were contacted. After the entire list was exhausted, a “snowball” sampling approach was used to identify additional stakeholders to contact with an interview request. The snowball sampling approach consisted of asking confirmed interviewees to supply the names of respected experts in their fields. An invitation email was then sent to the recommended experts. We also conducted additional searches to identify experts in relevant departments at academic and private sector institutions, and we contacted corresponding authors of relevant journal publications. In total, 308 cancer researchers were contacted to solicit an interview.

### *Informed Consent*

Following confirmation of agreement to participate in the interview, participants were provided with the consent form and interview questions via email. Included in the consent form was an introduction to the study; an invitation to participate voluntarily; a description of the research question in lay terms; an indication that the research intervention will be through an interview; an indication of study duration, risks and benefits; and a confidentiality statement. Each participant was asked to sign and return the consent form via email or fax prior to the telephone interview. An electronic and original signed copy was retained for the record.

### *Interview Procedures*

Final approval of the interview materials was received from the NCI on July 14, 2014, and interviews commenced immediately. Telephone interviews were scheduled for July through September 2014 based on the availability and preference of the interviewee. The team of interviewers included trained, experienced individuals who were conversant with the topic of mouse models and cancer research. During the interviews, the interviewers ensured that all required questions were addressed adequately and issues were probed further when necessary before the interview was concluded. The following questions were asked during the interview:

#### Interview Questions

1. Please indicate your title and role in your organization. How long have you served in this role?
2. In what capacity do you use mouse models, human-in-mouse models, or data generated from them in your current work (or former work history)?
3. From your perspective as a [academic basic, translational, clinical, epidemiological, private sector] researcher, what research questions need to be addressed using translational mouse models (e.g., type of cancer, specific signaling pathways)?
4. Please describe any emerging opportunities for fully integrating mouse models or data from mouse models in [academic basic, translational, clinical, epidemiological, private sector] research applications (e.g., cutting-edge human-in-mouse experiments, computational methods).
5. What current challenges exist to fully integrating mouse models in [academic basic, translational, clinical, epidemiological, private sector] research applications, and how can these challenges be addressed (e.g., technology needs, supporting infrastructure, databases)?
6. What capacity, knowledge, and skills does the [academic basic, translational, clinical, epidemiological, private sector] research community need to develop to make the best use of



mouse models as translational research tools (e.g., improved study design, training, statistical analyses)?

7. What collaborations can be developed to foster best practices for pre-, co- and post-clinical applications of mouse models?

Two follow-up questions were asked to ascertain the interviewer's interest in participating in a subsequent focus group and to elicit recommendations for additional stakeholders who might be willing to participate in the NCI's study.

Written notes on important quotes and wording suggestions were taken during the interview. As a backup to the notes, the interview was audio recorded to ensure that all expert input was captured accurately. The interviewers prepared a summary of each interview within 48 hours of its completion. Keywords and phrases were highlighted in the interview records to facilitate the analysis of key ideas and comments and to identify repeating themes among interviewees. The records were retained as an essential source of raw data.

Multiple procedures were implemented to ensure that the interviews were conducted consistently, documented appropriately, and interpreted correctly. Each interviewer received a list of common terms and acronyms related to cancer and mouse models, a summary of background information about the history of the MMHCC and purpose of the NCI Stakeholder Satisfaction Telephone Survey, links to the relevant NCI Funding Opportunity Announcements, and an interview guide. The interviewers also received detailed procedures for contacting stakeholders, scheduling interviews, documenting consent, and recording the interview results. Control sheets were used to track pending and completed interviews, as well as the status of signed consent forms. Throughout the interview process, procedures were reviewed regularly for ways to increase efficiency.

The interview results were monitored regularly to ensure the validity and integrity of the data throughout the process. All results were reviewed by the Project Manager within 72 hours of the interview to identify any topics for further clarification. If any interview response needed clarification, the stakeholder was contacted to request additional clarity or additional research was performed.

### *Data Analysis*

The information collected from the stakeholders was pooled and analyzed to develop a profile of community needs. As described above, interview discussions were recorded and summarized following each conversation. A spreadsheet was designed to capture responses to each interview question. Key topics, novel ideas, and identified priorities were extracted from each interview and analyzed to identify common themes that emerged during the conversations. The themes mentioned by stakeholders fell into five logical groupings: *Research Questions and Emerging Opportunities*, *Mouse Model Improvement*, *Cancer Research Community Resources*, *Development of Tools and Techniques*, and *Collaborations*. A qualitative assessment of the interview responses for each of these five themes is reported below. One analyst reviewed and evaluated all of the interview responses for consistency, and a second analyst reviewed the thematic groupings. All responses were anonymized for this report.

After completion of all interviews, each interview response was coded according to mention of 36 different keywords and phrases (Appendix D). The analysis evaluated the number of times a key issue was mentioned in an interview and by how many stakeholders among the five groups, enabling a quantitative comparison of priorities for the cancer research community across all stakeholder groups. Again, one analyst coded the interview results, and a second analyst confirmed the coding assignments. The results from the interview data analysis will be used to shape the development of focus group questions and inform subsequent focus group discussions.

## RESULTS

The interviewees were selected to ensure adequate coverage of cancer topics, institutional participation, and technical expertise within the list of stakeholders. This approach ensured that the NCI would capture the needs from the broadest possible range of the cancer research community. All interviewees emphasized the importance of using mouse models for translational research.

### *Response Rate*

The response rate to the request for interviews varied by stakeholder group (Table 1), but was uniformly low. The low response rate necessitated a significant investment in identifying additional interviewees, as described above in Methods: Stakeholder Recruitment. The stakeholder group with the lowest number of interviews was the epidemiologists, who were the least likely to have experience with mouse models and might not have realized the value of contributing their insights to the NCI needs assessment. In fact, several potential interviewees responded to the invitation email indicating that they lacked the expertise required for the interview. In these cases, the purpose of the interview and the relevance of epidemiological input were communicated to the individual, and several researchers subsequently agreed to interview. Because of the difficulty in identifying individuals with expertise in cancer research, epidemiology, and mouse models, it was not possible to reach 20 interviews in the epidemiology group. Interviews were added to the clinical and private sector stakeholder groups to reach 100 total interviews.

*Table 1. Response rate to interview requests.*

<b>Stakeholder Group</b>	<b>Number of Experts Contacted</b>	<b>Number of Experts Interviewed</b>	<b>Response Rate</b>
Basic	56	20	36%
Translational	75	20	27%
Clinical	69	21	30%
Epidemiological	49	15	31%
Private Sector	59	24	41%
<b>Total</b>	<b>308</b>	<b>100</b>	<b>32%</b>

### *Stakeholder Characteristics*

Of all interview respondents, 66 percent were male and 34 percent were female. This proportion of male to female respondents approximates the national average for tenured and tenure-track faculty in academic institutions (68% male and 32% female\*). No data were collected on respondent age, but career stage can be used as a loose proxy to approximate age. Although experienced researchers were sought for their opinions informed by years of experience, junior investigators also were included in the study to ensure that all perspectives were captured. As shown in Appendix E, the career stage of the respondents ranged from Assistant Professors to Department Chairs and Deans. Several Chief Executives representing private sector organizations contributed their insights, along with Vice Presidents and Directors.

Interviewees were selected from all geographic locations representative of the United States. Although the inclusion of significant numbers of international researchers was avoided, a few international researchers were interviewed to provide an outside perspective. A wide range of institutional affiliations of the selected interviewees (Appendix E) ensured the generalizability of the results. Interviewees from the academic sector represented a variety of R01 research institutions (e.g., Harvard University, University of California). Private sector interviewees were selected from large pharmaceutical companies

\* National Science Foundation Survey of Doctorate Recipients, 2013.  
[http://ncesdata.nsf.gov/doctoratework/2013/html/SDR2013\\_DST20.html](http://ncesdata.nsf.gov/doctoratework/2013/html/SDR2013_DST20.html)

(e.g., Novartis), contract research organizations (CROs; e.g., Biomodels), and private research institutions (e.g., Cold Spring Harbor Laboratory).

By design, all of the interviewees had working knowledge of the use of mouse models in translational research. Stakeholders representing a wide range of cancer research topics (e.g., type of cancer, specific signaling pathway) were selected across a variety of research stages (e.g., basic, preclinical, clinical). As depicted in Appendix E, respondents demonstrated expertise in the most common cancers (e.g., breast, lung, prostate, and colorectal), as well as many others. Many of the scientists focused on adult cancers, while others studied pediatric oncology. Stakeholder interests spanned tumor initiation, progression, and metastasis. Specific topics of focus include tumor suppressors (e.g., p53) as well as oncogenes (e.g., cMYC, KRAS, PI3K).

The interviewees also represented a broad scope of expertise regarding the use of animal models in their research projects. The experience tracked closely to the assigned stakeholder groups. For example, basic, translational, and clinical researchers had direct experience using GEMMs, PDX, and other types of mouse models in their research programs, while epidemiologists primarily worked with biomedical informatics or engaged in collaborations with investigators who used mouse models. Many epidemiologists use mouse data frequently in their work. Basic researchers tended to be those who built GEMMs or used mouse models to develop biomarkers, and clinicians tended to use PDX models in their research. Private sector researchers typically managed mouse model experiments during the drug discovery process.

## COMMON THEMES

Common themes emerged from all of the stakeholder groups. Indeed, responses were more alike than different across groups. Thus, this report is organized by common theme across all stakeholder groups, followed by sections for issues specific to academic basic, translational, clinical, epidemiological, and private sector researchers. The responses fell into five general categories loosely aligned with the interview questions:

- I. [Research Questions and Emerging Opportunities](#)
- II. [Mouse Model Improvement](#)
- III. [Cancer Research Community Resources](#)
- IV. [Development of Tools and Techniques](#)
- V. [Collaborations](#)

*Research Questions and Emerging Opportunities* includes specific topics that scientists mentioned as warranting additional research in the categories of translational research and drug discovery. The *Mouse Model Improvement* category comprises suggested priorities for developing models that more accurately represent human disease. *Cancer Research Community Resources* includes themes related to research and institutional capacity that should be augmented within the cancer research community. The *Development of Tools and Techniques* category is composed of specific methods and practices that should be pursued to facilitate translational mouse research. The *Collaborations* category includes high-priority partnerships that stakeholders indicated should be fostered to advance the field.

### I. *Research Questions and Emerging Opportunities*

The stakeholders identified research questions and emerging opportunities for the use of mouse models that encompassed the scope of translational research, from understanding basic signaling pathways to lead drug optimization. The interviewees discussed the importance of mouse model research in basic,

preclinical, and clinical applications. A sample of the responses indicate that mouse models are critical to—

- Understand the genetic and genomic hallmarks of cancer.
- Elucidate the function of genes involved in the development and progression of cancer, including gain- and loss-of-function mutations. Mouse models are used to conduct genetic experiments to validate new hypotheses generated through human genomics studies.
- Conduct preclinical trials that are less expensive and faster than human studies. Animals provide a simplified system to seek answers to challenging questions; the results can then be tested in more complicated systems.
- Test new therapies, especially combination therapies.
- Understand the life history of cancer, which requires access to the disease at many stages and is not usually possible in human patients.
- Trace cell lineages in normal development and from clonal cells through the use of reporter alleles.
- Generate hypotheses, as models with a tumor-causing gene can provide new and unexpected insights into cancer biology.
- Validate *in vitro* findings.
- Make translation more efficient.

Many of the researchers queried used both GEMMs and transplantation models (e.g., syngeneic, xenograft, or PDX models) to address their research questions. Some investigators, however, expressed a preference for GEMM or PDX models. The benefits of GEMMs include an intact immune system, defined genetic background, and spontaneous tumors in the correct location. PDX model benefits include a better representation of the patient condition.

Researchers identified nearly all stages of cancer as important for study, with an emphasis on tumor initiation and metastasis. Many investigators mentioned specific research topics that could be addressed using translational mouse models (e.g., inflammation, angiogenesis, microbiome). Several specific topics were mentioned by multiple investigators, thereby warranting a higher priority. These research topics and emerging opportunities clustered into two themes: Translational Research and Drug Discovery.

## Translational Research

The topics in the Translational Research category comprise areas that were mentioned by multiple investigators relating to the use of mouse models in myriad research applications, ranging from basic to clinical. These include the following topics, each described in more detail below:

- Gene Function and Signaling Pathways
- Genomics
- Epigenetics
- Biomarkers
- Tumor Heterogeneity
- Tumor Microenvironment
- Immunology
- Natural History
- Cancer Prevention
- Personalized Medicine
- Systems Biology

- Environmental Exposures and Risk Factors

### **Gene Function and Signaling Pathways**

Mice are used to illuminate disease associations and determine how specific genes contribute to disease. Scientists then use the mice to characterize the functional relevance of gene variants associated with risk for cancer. Investigators use mice to study basic signaling pathways in cells; mice can help address almost every biological question about single-gene effects—and the effects of turning genes on and off. Some mouse models are useful for studying signaling networks, rather than specific types of cancer. Mouse models can be used to identify drivers of cancer, and models can be engineered to express oncogenes in the same way that they are expressed in human cancers to better define the biological significance of certain mutations. Epidemiologic studies, with the advancement of technology, are finding previously unknown molecules, pathways, and genes that have shown consistent association with disease features but whose exact function or activity is unknown. Examining an animal model can help illuminate the mechanisms.

### **Genomics**

A comprehensive understanding of mouse tumors can be gained through genomic data. There is a need to sequence mouse tumors and then use the resulting information to test hypotheses, leading to an improved understanding of the genomic events that drive cancer growth and metastasis. In mice, scientists can control for the genetic background and examine the effects of specific mutations. Genomic analyses present a tremendous opportunity to study the genetic heterogeneity of tumors. Mice also can be used to stratify cancer types by genotype.

Large cancer genome sequencing projects, such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium, are identifying long lists of genetic alterations that are observed in human tumors, and it is a challenge to prioritize the most important mutations that should be pursued as drug targets. Mice can be used to evaluate which alteration or combinations of alterations has the biggest impact on the development of cancer, because the exact mutation can be controlled in mice. Mice also can be used to prioritize driver genes identified in a genomics project. An opportunity exists for the NCI to survey grant awardees to determine which mouse models are needed to inform the development of high-priority models.

### **Epigenetics**

A promising research area is the study of epigenetic changes during cancer development. A significant opportunity is to study the effects of epigenetic inheritance of cancer risk. The evidence surrounding testicular cancer, for example, suggests a strong role of epigenetic inheritance. It is not possible to study this question in humans because genetic background and environmental exposures cannot be controlled; furthermore, the time scales necessary for multigenerational studies are too long. Mouse models allow a careful control of genetic background and environmental exposures, enabling researchers to isolate the contribution of epigenetic inheritance to phenotypic outcomes. The role of diet and epigenetics in the prevention of cancer is another area receiving a lot of attention. Inducible models that replicate the inflammatory response that leads to genetic and epigenetic changes in cancer are needed.

### **Biomarkers**

Mice can be used for development of cancer imaging biomarkers and tracers. The goal is to develop biomarkers for certain genetic events (e.g., expression of mutant p53 or KRAS). Several investigators cited an emerging opportunity to study precancer biomarkers for prevention and detection. Biomarker studies in mice can be used to predict response to therapy, and mouse models can provide information about potential biomarkers that may be relevant to humans.

### **Tumor Heterogeneity**

Many investigators are interested in studying the relationship between genetic heterogeneity and response to therapy. A major limitation of GEMMs is the lack of complexity and genetic heterogeneity; PDX models more accurately reflect the heterogeneity of disease. Studying heterogeneity is important in understanding recurrence and tumor evolution, as well as establishing subgroups of tumors likely to respond to treatment. Heterogeneity in a mouse model, however, can present challenges for statistically meaningful data.

### **Tumor Microenvironment**

One advantage of GEMMs is that scientists can manipulate specific genes in particular cell types to study the interaction between the tumor and other cells in the local environment (e.g., immune cells, fibroblasts). Scientists mentioned the need to study epithelial-stromal interactions in basic and cancerous development. Specifically, researchers cited the need to understand how neighboring cells interact with the tumor, and how reciprocal signaling influences tumorigenesis. Understanding the communication between different types of cells can help generate hypotheses for future studies. Investigators also must determine ways to target the tumor microenvironment and test the importance of therapeutic effects on the tumor microenvironment. The interaction between cancer cells and the environment is easier to study *in vivo*.

### **Immunology**

Several investigators use mice to study the immune response to cancer, including immune-mediated killing of cancer cells. An outstanding research question is how well the models reflect tumors in humans, especially with respect to the immune response. Immunocompetent mice with syngeneic transplants are needed to better reflect the genetics of human cancer. Currently, no models are truly predictive of the efficacy of immunotherapies.

### **Natural History**

Mouse studies are useful for understanding the natural history of cancer, including tumor initiation and metastasis. The timing and number of mutations and the mechanisms facilitating tumor progression were several of the cancer mechanism topics that arose frequently. Mice can be used to identify genetic predispositions and other factors for certain cancers. Many investigators study the “cell of origin” question and noted a need to better understand the properties of tumor-initiating cells and how they create prolific cancer growth. The cell of origin must be targeted to prevent cancer recurrence. In addition, studying the early stages of tumorigenesis can help researchers understand how to prevent tumors from forming. Related to tumor initiation, the study of cancer stem cells and dormant cancer cells was deemed important. The prevention of metastasis and containment of tumor growth after metastasis was cited as another important emerging need for the cancer research community. Metastasis, like tumor initiation, is difficult to study *in vitro*. Almost all current treatments target primary tumors; drugs must be tested in metastatic settings.

### **Cancer Prevention**

Mouse models are used to examine how cancer develops and how to prevent it. They also can be applied to study the reversal of preneoplastic changes; these experiments cannot be completed with tissue culture experiments. Scientists are interested in understanding the events leading to tumor formation and the consequences of intervening at different stages. Animal models are useful for investigating early stages in cancer development prior to invasion when cancer is formally declared by a pathologist. Integrating an epidemiologic approach can help to identify markers in humans early in carcinogenesis and test those in the mouse for prevention studies. One big issue related to prevention and early stage preinvasive neoplasia is that few investigators are devoted to that work, according to one interviewee.

### **Personalized Medicine**

Every tumor is unique, and subcategories of tumors can be modeled in mice to understand human cancers. A suite of mouse models can recapitulate many mutations in patients. Many investigators are studying the molecular properties of human tumors in mice to ensure that they resemble the molecular profiles of individual and groups of patients. The advent of PDX technology allows scientists to screen many therapeutic agents in one model to determine which drugs might work best in patients. Scientists are pioneering an “avatar” system as a means to do personalized preclinical testing to aid in treatment decisions, but the validity of this approach needs to be tested prospectively. The avatar system involves the excision of patient tumors and implantation into murine hosts, which provides the possibility to test therapeutic effects in a laboratory experiment and apply knowledge to the actual patient. Genomic sequencing can also be used to develop personalized treatments.

### **Systems Biology**

Cancer is a system-level problem, and it is important to understand how cells interact with each other. Mouse models provide a useful platform for systems biology; many basic questions about physiology and development can be studied in animals. Tumor cells behave differently *in vitro* than *in vivo*, and it is important to have a robust model for drug discovery that represents how drugs respond in a living tissue. One investigator noted that cancer geneticists tend to focus on genes, but there is a need to better understand protein signaling networks and mechanisms of drug response, which requires that system biology approaches be incorporated into mouse model studies. Cancer can be studied not as proliferating cells, but as an ecosystem involving multiple cellular and extracellular components that contribute to the development of disease. Using a biological systems approach can help identify pathways to obesity and metabolic syndromes and what is required for preventive approaches.

### **Environmental Exposures and Risk Factors**

Mice can be used to test the effect of environmental exposures, including early exposures, on development and carcinogenesis to recapitulate the genetics of human disease in response to environmental exposures (e.g., ultraviolet radiation or smoking). Dietary or exercise intervention questions can be studied in the mouse, and it is easier to test combined exposures, which more accurately reflect how people live. One investigator emphasized that chemically induced carcinogenesis in mice is more likely to replicate the process that occurs in humans. Thus, mouse models can be used to identify risk factors by testing potential chemicals as carcinogens, and the results on carcinogenic risk can be extrapolated to humans. A researcher noted that it would be helpful to evaluate risk models from human population studies and develop a mouse model to perform a similar assessment.

### **Drug Discovery**

The research topics in the Drug Discovery category include topics relating to the use of mouse models primarily in clinical, translational, and private sector research applications. For example, mice are used extensively for preclinical drug discovery, including the identification and development of therapeutic targets. Interviewees recommended prioritizing mouse model research at every stage of the drug discovery process, from biomarker development to therapeutic validation. Robust preclinical testing was cited as a prerequisite for promising clinical applications; mice provide a rational way to move potential therapies to the clinic. Scientists uniformly commented that *in vivo* studies are superior to *in vitro* studies for clinical applications. Specific topics relevant to drug discovery mentioned by multiple stakeholders are described in more detail below:

- Diagnostics
- Mechanisms of Action
- Efficacy

- Toxicity
- Resistance
- Lead Optimization
- Drug Combinations
- Patient Selection

### **Diagnosics**

Mouse models can be used to study early detection of cancer. Early indicators of cancer (e.g., neoplastic lesions, benign tumors) cannot be studied in humans, but can be studied in GEMMs to test imaging modalities or serum markers to identify and define cancer precursors.

### **Mechanisms of Action**

Mice are used to study the mechanisms of drug action, including the bioavailability of the drug and how the compound affects physiological functions and tumor maintenance. Mice are used to understand how the drug behaves in an *in vivo* context. Understanding the mechanisms of action of drugs is needed to validate the representativeness of human tumor types. Researchers use mice to ensure that the drug gets to the correct organ, hits the target, and triggers a pharmacodynamic response.

### **Efficacy**

Mice are used throughout academia and the private sector to evaluate the efficacy of new drugs and to optimize existing therapies. Mouse models can help investigators understand the kinetics of a treatment (e.g., an immediate or delayed effect).

### **Toxicity**

Drug toxicity is an important consideration. If a private sector company identifies a robust response to a drug in reducing tumor growth, but the patients stop taking the drug because of negative side effects, the drug is useless. Mice can be used to study the toxic effects of radiation and other therapies on healthy tissue. For example, robust mouse models are needed to determine which parameters enhance the effect of radiation on the tumor while protecting normal tissues. Mice can be used to identify adverse effects of drugs when developing a safety profile of clinical applications of drugs. Treatment response and toxicity should be addressed simultaneously. Therapy doses and schedules can be adjusted to minimize side effects and maximize efficacy.

### **Resistance**

The development of resistance to treatment is an important research avenue. There is a need to understand how cancers evolve during treatment and develop mechanisms of resistance. Mice are valuable models because they develop resistance mechanisms faster than humans. Typically, information about mechanisms of resistance, including the genetics and signaling pathway, translates accurately to humans. Mouse genetic parameters also can be correlated with drug efficacy and resistance. Another research need involves discovering combinations of drugs that will prevent tumor escape.

### **Lead Optimization**

Mouse preclinical trials can be used to prioritize which compounds move forward to human clinical trials during the lead optimization process. Animal models help decide if an early technology or drug warrants further development, as it is important to focus limited resources on the targets most likely to alter the natural history of disease. Mice also are good models to test drug dosing and schedule strategies for lead therapeutics under development.



### **Drug Combinations**

The study of how and when to use various combinations of drugs is an emerging opportunity. Single agents are effective, but rarely curative in cancer. The current interest is in identifying effective therapeutic combinations, and mouse models support that endeavor.

### **Patient Selection**

Mouse models are used to evaluate patient selection hypotheses for the clinic. In the drug discovery process, mouse models can be used to identify which target population—identified by biomarkers or genetic background—might benefit from which drug. Mice are useful for understanding the subcategories of patients likely to respond to a specific treatment.

## **II. *Mouse Model Improvement***

Cancer research stakeholders indicated that mouse models typically have not been as predictive as they should be, and it is important to develop models that are more representative of human disease. Early mouse models, in particular, did not reflect the human situation, and more advanced and accurate models are necessary.

There was a discrepancy between some investigators who felt strongly that the NCI should focus on models and pathways that relate to greater number of cancer patients, and others who believed that efforts should focus on diseases, including rare diseases, for which no model currently exists. Developing models of these diseases was suggested as a high priority because the field is missing opportunities to study the conditions due to the lack of research tools. Specifically, researchers mentioned the need to invest resources in studying pancreatic cancer (survival has not improved significantly in 25 years) and triple-negative breast cancer (which has no targeted therapeutics and is very heterogeneous).

The engineered mutations must be relevant to the tumor type studied, mice must be engineered to manipulate gene expression in specific cell types, and better imaging techniques are needed to understand events at the single-cell level. Researchers suggested several ways in which models can be improved, addressing the challenges and opportunities for each topic. A description of each type of model improvement follows:

- Model Relevance
- Characterization and Validation
- Accurate Models
- PDX Models
- Humanized Mice
- Comparative Biology
- Population and Exposure Models
- Models of Late-Stage Disease
- Other Models

### **Model Relevance**

Some mouse models are not representative of the human cancer that they are designed to address, leading to a lack of clinical translatability: Success in the model does not guarantee success in the clinic. This issue arose many times throughout the interviews. For example, experiments in mice might indicate that the target exists and the treatment works, but when advanced to the clinic the novel molecular therapies may fail in humans (e.g., monoclonal antibodies, tyrosine kinase inhibitors).

## **Challenges**

There is a need to determine whether the mouse models accurately recapitulate human disease and to investigate why targets identified through mouse studies frequently do not translate to human studies. Building representative models, however, is more complicated, expensive, and time-intensive. Less predictive models are cheaper. Scientists need to be convinced that the cost and time investment are worthwhile for more predictive models.

Current animal models need to be more rigorous, and the field needs a better understanding of what each model represents and how it can be aligned to the appropriate patient population. In fact, a major weakness of mouse models is that they do not recapitulate the entirety of human disease. Often they represent specific aspects of human disease, but not enough work has been done to clarify which aspects of disease are represented by the models. An additional challenge is that some human cancers—such as prostate cancer—do not occur naturally in mice. Identifying suitable models for studying such diseases is important.

## **Opportunities**

It is important that the next generation of mouse models provide higher predictive utility in drug studies. Cancer research stakeholders placed value in further developing GEMMs, PDX models, or both to better recapitulate disease. Indeed, technology for GEMMs and xenograft models is improving. Rather than building entirely new models, it might be more efficient to cross existing lines and look for advantages in translatability. The cancer research community is working to combine and synergize models to improve their usefulness.

Several investigators expressed a desire to explore the fidelity of various mouse models for the study of human cancer. Clinical trials should be developed to determine whether models recapitulate the features of the disease in human patients.

As new technologies become available, scientists are becoming better at selecting relevant models. For example, mRNA profiling in xenograft models has helped scientists identify models that are more relevant to the drug under development for a particular patient population. These platforms and technologies should be utilized to increase the understanding of both current models and models that scientists want to develop.

There is an opportunity for increased awareness of the relevance of particular models. The research community needs to realize that each type of cancer in humans (e.g., breast cancer) represents a broad spectrum of pathological and molecular subtypes. A mouse model will not represent the entire spectrum. Experience shows that if a model can be identified to study a specific subtype, it produces valuable results.

## **Characterization and Validation**

The lack of standardized characterization of mouse models (e.g., GEMM and PDX models) was mentioned frequently as a barrier to selecting the best model.

## **Challenges**

The community needs to better characterize existing models and determine how well they recapitulate human disease. Most scientists do not spend much time validating models; funds are not available for detailed characterization. Additionally, investigators often are not careful enough with the translation of

mouse models, translating findings to the clinic before the models are validated adequately. A related key need is the validation of mouse models using primary human cancer cells *in vitro*.

The lack of reproducibility of experimental results is another concern that was cited often. Initial and repeat validation of experiments should be pursued to ensure better reproducibility between experiments.

### **Opportunities**

Complete characterization and validation of animal models is necessary. Similar to analyses that have been performed in cell lines, models should be characterized for genomics, metabolomics, and proteomics. Investigators need to fully study the phenotypes of the tumors that arise in the mouse. Improved methods may need to be developed to facilitate better tumor characterization. The cancer research field should establish several highly credentialed models, as well as many more cutting-edge models that represent a greater variety of targets and test new ideas, according to one researcher. A granting mechanism could be revised to ensure that models are adequately qualified after development.

Scientists should validate models and ensure appropriate experimental endpoints mirror those in the clinic. To increase the representativeness of a model, some companies design experiments to *post hoc* recapitulate the clinical model. This process is very expensive, but further clinical development is justified. Similarly, drug profiling tests should be pursued to characterize how standard-of-care drugs work in the mouse. A mechanism is needed to integrate development of mouse models with pre-, co-, and post-clinical research.

Reproducibility of the animal models can be pursued through initial and repeat validation of experiments. Dedicated reproducibility efforts, such as the replication studies conducted by the Center for Open Science, would help to address the concern of poor experimental reproducibility. The genetic background should be considered when comparing experimental results between mouse strains. Efforts to develop live cell banks from patient tumors should be expanded to help with validation efforts. There is tremendous information from human tumor sequencing efforts.

### **Accurate Models**

The development of more accurate and precise mouse models was cited as an important need by cancer researchers, who seek to advance the frontier of modeling through improved GEMMs, mouse-in-mouse, and human-in-mouse models.

### **Challenges**

Accurate models tend to be more expensive and time-intensive to build. One investigator noted the limitation in mouse models is the reliance on knockouts, given that most mutations in human cancers are not equivalent to knockouts. Another scientist questioned the fidelity of transgenic mice with overexpressed oncogenes, and whether those models were truly representative of human cancer. Transgenic mice only reflect the initiating mutation, and often do not represent the series of mutations that develop over time in a human cancer. Researchers would like to use transgenic models where the disease originates in the appropriate organ.

### **Opportunities**

There are now more precise mouse models, where genes are mutated in small groups of cells rather than the entire animal. This provides a more realistic view of how tumors form, although the animals are more expensive and complicated to build. These models, however, will produce better data. The generation of more precise models should be pursued through new technology, such as the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology. Many investigators emphasized the need to

generate mutations relevant to specific tumor subtypes to accurately reflect patient populations. Targeting mutations to specific cell types is another approach to create more precise models that more accurately represent human cancer.

## **PDX Models**

Many investigators identified PDX as an emerging opportunity. PDX demonstrates a move away from artificial cell lines, and many companies use PDX models as a basis for drug discovery decisions.

### **Challenges**

PDX models are more expensive, and they still tend to be seen as a research tool rather than an immediate therapy meant for an individual patient. Another limitation to the use of PDX is the requirement for immunocompromised mice, which might not represent human disease accurately because an intact immune system plays an important role in fighting cancer. Furthermore, immunocompromised mice cannot be used to test immunotherapies. Cytokine and growth factor function is often different between the two species, which can be a challenge for leukemia studies in particular. The use of heterotopic implantations of cell lines and PDX for the purpose of screening novel compounds for anti-cancer efficacy should be more thoroughly evaluated.

PDX models are insufficiently annotated. There is a need to bring together all of the available PDX models, characterize them, and distribute the information so that investigators are aware of the best models to address specific questions.

Interviewees identified a need to understand genetic drift, particularly in PDX models. PDX culturing procedures vary, and drift over time is a concern. Researchers need to determine how often the PDX models should be sequenced to measure drift.

### **Opportunities**

Many investigators identified PDX as an emerging opportunity. Complementing mouse-in-mouse xenografts with human-in-mouse models allows scientists to address questions about the way heterogeneity affects response. For example, if a population of tumor cells has different genetic features, what subpopulation of those cells will respond to treatment? PDX models also allow clinicians to test if a therapy works in individual patients. As PDX models become more available, the system can be perfected to make a model physiologically and clinically relevant to the human situation. There is a need for simpler methods for making treatment decisions, which can be resolved by developing highly characterized PDXs that can be used to test the efficacy of a specific agent and then applied back to the human population.

PDX models are superior to implantation of human cell lines in mice because those latter tumors do not resemble those in the human patient—they are extremely prolific and survive under environmental conditions atypical of mice and humans. A lack of heterogeneity of models has been a common criticism of GEMMs, and PDX models address this concern by capturing the diversity of the patient population. A caveat, however, is the lack of immune system in most PDX models. Humanized PDX models attempt to address the contribution of the immune system in tumor growth and metastasis, but they are expensive and difficult. These models should be developed further.

Several investigators suggested creating a consortium of PDX researchers to develop best practices and work through challenges in the field. Standardization of approaches will facilitate comparison of results. Scientists should collect complete patient information when developing PDX models from a tumor to improve the annotation and understanding of the model. If patients consent to link the data about their

tissues, more information can be gleaned from the mouse to inform which clinical trials would be most beneficial to the patient. One approach mentioned is for the NCI to receive the PDX models, characterize the cells, and then provide the model to the community. A library of PDX samples available to the community, with pathology and genotype information, would be very helpful.

## Humanized Mice

The immune system plays a key role in both metastasis and response to treatment, and current immunosuppressed models cannot replicate this. Humanized mice—immunocompromised animals with engrafted human immune cells—provides an opportunity to address many concerns.

### Challenges

The lack of an intact immune system is a challenge in immunocompromised models used for PDX and other xenograft experiments. Many researchers commented on the difficulty of establishing a realistic understanding of a therapeutic response in an immunocompromised animal. The problem is particularly critical for immuno-oncology, where an intact immune system is critical to accurately represent a drug response. There is a need for immunocompetent mice that can sustain human tumors.

### Opportunities

Many researchers mentioned the emerging models that contain a human immune system component as critical in advancing the field. Humanized mice can assist with understanding the role of the immune system in tumorigenesis and in therapies; the immune system needs to be studied *in vivo* and dynamically over time. They also can be studied to assess whether certain genotypes are associated with adverse outcomes following transplants. Signaling pathways, cytokines, and the maintenance of lymphatic vessels can be studied in a humanized mouse. The new field of immuno-oncology activates the patient's immune system to fight cancer. Humanized mice are helpful to determine potential safety risks and the potential for monoclonal antibody drugs in immuno-oncology.

## Comparative Biology

Scientists need to understand the differences between mouse and human at the gene and phenotype level to better predict how results from mouse experiments will translate to the clinic.

### Challenges

Many proteins expressed in humans are not perfectly mimicked in the mouse, and vice versa. This poses a challenge (i.e., mice cannot recapitulate all aspects of human disease) as well as an advantage (scientists can distinguish between human and mouse proteins for use as internal or negative controls in experiments). Careful comparative biology of mice and humans is needed, yet grant support is insufficient for descriptive experiments that assess how closely mouse models resemble the human disease process. A funding mechanism is needed for foundational work of comparing mouse and human biology. Mouse models raise interesting questions, but those questions often are not related to or generated from epidemiologic or clinical studies in humans.

### Opportunities

Generating comparisons of mouse and human data is one approach to address the concern about differences in mouse and human biology. Using mouse gene expression data to correlate with human data can help to identify common targets. Mouse and human data should be compared on the basis of genetics, therapeutic response, and toxicity profiles.

Differences between mouse and human biology should be acknowledged and documented, rather than ignored. Citing relevant differences in publications is especially critical; many high-profile publications often lack critical review of the models. Research projects should consistently compare human patients to the mice that are studied. Several investigators cited the need to determine why treatments developed using mouse models fail in the clinic.

Comparative oncogenomics approaches and production of orthology maps will strengthen the ability to identify specific networks (especially nodal points that represent evolutionarily conserved proteins) and see to what extent human and mouse networks overlap. Seeing the same effects in human and animal tissues provide more confidence in the research finding.

Next-generation sequencing can be used to gain systematic and unbiased assessments from both mouse and human data, which can be compared to ascertain similarities and differences. Bioinformatics approaches should be developed to harmonize data extracted from mouse and humans. Data analytics, such as search algorithms and databases that make use of integrated human and mouse data sets, are important for moving research findings to clinical trials. A thorough genomic evaluation of a limited number of mouse model tumors would permit a comparison to humans. Several investigators mentioned the need for a TCGA equivalent for mouse tumors that would enable the mining of data and selection of the most appropriate mouse model, leading to a personalized approach to clinical trials and medical practice. Another opportunity is to leverage the international effort to knockout individual genes in mice to study phenotypes across a wide range of tissues, known as the International Mouse Phenotyping Consortium (IMPC). The project is generating a database in which hits are linked to various human disorders. The databases are based on mouse studies, but allow researchers to perform analyses without studying the mice themselves. This data set can be valuable in improving the understanding of cancer genetics.

Epidemiological cohorts are beginning to perform molecular profiling on their deeply annotated samples, and it would be helpful for epidemiological researchers to have access to similar data sets in mice. The interaction of those two data sets is likely a rich data source.

## **Population and Exposure Models**

Cancer researchers cited the need for improved population and exposure models to better represent human genetic variability, as well as to represent human exposures more realistically.

### **Challenges**

Most models for cancer risk factor research were developed many years ago and rely on artificial exposures, limiting the insights that can be gleaned. There is a need to recapitulate more realistic human exposures; it would help researchers to develop more accurate models that develop human-like disease when exposed to cancer-associated exposures common in the human population (e.g., UV, tobacco, physical inactivity, unhealthy diets). Scientists know that there is interaction between genetic and environmental factors, but they have not been able to create models that look at both genetic and environmental factors. Animal models are useful in this regard.

### **Opportunities**

There are more than 200 potential risk factor loci already identified through genome-wide association studies (GWAS) that have not been functionally characterized; mouse models are critical to exploring the genetic risk. The poor prediction of disease risk and treatment could be addressed with population models that have demonstrated predictive and therapeutic utility. Mouse population models, such as collaborative cross models, tend to be more representative of human disease. The cancer research community requires

large genetic reference populations of mice to model the genetic complexity of patient populations. Studies should be performed on complex populations of animals that are diverse for age, gender, and other characteristics. Applying sophisticated statistics, such as approaches used in epidemiology, will ensure translational benefits. Population models are inherently collaborative; researchers can integrate data across studies (genenetwork.org) or include data from other sources.

Humans live in a world of combined exposures, and scientists are interested in models that combine exposures to multiple toxicants at the same time. They also would benefit from a model that could show interactions between genetics and the environment (e.g., social stressors, toxicants) and allow researchers to quickly test environmental factors in the animal model.

## Models of Late-Stage Disease

Many stakeholders lamented the reliance on treatment-naïve models for important translational experiments.

### Challenges

One important limitation is that many mouse models are used to test naïve disease rather than refractory disease. Currently, most drugs are tested on mice that have not undergone chemotherapy or radiation. In contrast, patients in human trials often have been treated previously with chemotherapy or radiation, which affects the drug response.

### Opportunities

The cancer research community identified a need to build models of refractory disease. Currently, the majority of models are derived from biopsies early in treatment history and do not represent late-stage refractory standard of care. Developing models that represent late-stage disease should be a priority.

## Other Models

Perhaps because the interviewees believed that the topic was beyond the scope of the NCI's assessment of the use of mouse models in the cancer research community, very few scientists mentioned the opportunity for developing other models to better understand human disease and address some of the limitations of mouse models.

### Challenges

Although mouse models are commonly used for translational research, important limitations (e.g., size, relevance to human biology) restrict their applicability for certain experiments.

### Opportunities

Several researchers cited the emerging opportunity of organoids, such as mammosphere or neurosphere cultures, in research applications. It can take 3 months for a primary tumor to grow in a mouse, and some patients do not have the luxury of time. High-throughput screening with mammosphere cultures can reduce the experimental time. Several investigators suggested broadening research efforts to other animal models, such as rats and large animals.

## III. Cancer Research Community Resources

Interviewees were queried about the capacity, knowledge, and skills that the cancer research community should develop to make the best use of mouse models as translational research tools. They generated a robust list of resources and cultural shifts that would encourage new investigators to adopt mouse models

and established investigators to ensure their appropriate use. The suggestions were grouped into the following categories:

- Education and Awareness
- Mouse Model Availability and Selection
- Core Facilities
- Pathology
- Standardization and Best Practices
- Funding
- Technology Transfer and Data Sharing

## Education and Awareness

The majority of the respondents indicated a need for increased awareness of the value of mouse model research, as well as educational opportunities to promote the appropriate use of mouse models in translational research.

### Challenges

A lack of understanding about the strengths and limitations of mouse models and related technology was an often-voiced concern. Mice are not perfect models for human disease, and researchers need to know the strengths and limitations of the models, as well as the strengths and weaknesses of the technologies used to study them. One limitation, for example, is that mouse models represent a small subset of patient tumors. Some agents—such as antiangiogenic drugs—work in mice, but not humans; the reason for this difference needs to be investigated.

Communication is another challenge. Researchers in the cancer field are not aware of specific, effective treatments that have resulted from mouse model research; these advances should be documented and publicized. The scientific community needs to be more aware of the usefulness of animal models in biomedical research and needs to exchange ideas and resources at the level that can advance the cancer research field. Furthermore, many epidemiologists noted that the research community is not aware of the possibilities for modeling epidemiologic exposures in mice.

Proper use of mouse models requires training. Education about and expertise in developing and maintaining mouse models are absent from many laboratories, which precludes expensive or complex experiments. Reproducibility in experiments is an issue, especially with more intricate PDX surgical procedures. Skills need to be taught to produce valid, reproducible data. More sharing of expertise within the cancer research community is vitally important.

A subset of the research community does not believe that GEMMs are useful. In the past, translational research has not been favored or supported. The clinical community, in particular, is not sufficiently aware of the power of mouse models, and many scientists are skeptical of preclinical mouse data. The scientific community—including the NIH, FDA, physicians, and researchers—needs to accept and endorse the value of mouse studies. Another cultural challenge is that there are too many rules and regulations concerning animal research, which increases the administrative costs and time necessary to conduct studies. Several researchers also noted a reluctance of some mouse modelers to embrace new technology. Although better models are now available, some scientists have been using the same models for years. These individuals should be educated about the benefits of using more advanced models.

Researchers called for an increased understanding of human disease and pharmacology (including toxicology and whole-body physiology), among other subjects. For example, a drug will not be useful for



a brain tumor if it cannot cross the blood-brain barrier—even if it targets the right mutations at the molecular level. The basic research community needs to better understand clinical trial design so that experiments in mouse models can be made relevant to human studies. For example, it is possible to do pancreatic biopsies in mice, but not as easy to do them in humans. Stakeholders also called for education and standard procedures related to the mouse environment. Being housed alone, which is common with male mice, is very stressful and leads to more rapid progression of tumors.

### **Opportunities**

Stakeholder suggestions related to education and awareness were categorized according to the following themes:

- Advocacy
- Communication
- Education
- Training
- Meetings and Workshops

#### **Advocacy**

Several investigators mentioned the need for advocacy within the cancer research community. Educating the community on the availability and value of mouse models for cancer research would be important in raising awareness. This education could take the shape of training workshops or meetings. Grant review panels, in particular, must be educated to realize the value of mouse models. Respondents noted both the need for clinicians to be educated about basic science and the need for basic researchers to be educated about clinical concepts. To better understand the limitations and advantages of mouse models, one investigator suggested convening the best modelers for an open and honest discussion to identify ways to improve translatability. This approach could be applied for several high-priority cancers. Journal editors should endeavor to ensure that authors explain the subset of patients to which the model applies.

#### **Communication**

Increased communication about the value of mouse models in translational research applications would elevate the visibility of the benefits of this type of research. Better communication will help investigators share mistakes as well as successes, which both produce useful lessons for future research. The United Kingdom Regenerative Medicine Platform supports research of various issues across disciplines and is a good model for communication. The NCI might adopt the role of reviewing and communicating critical breakthroughs in mouse model work. Regular reviews of the literature will help identify models and research with the greatest translational potential (e.g., new reporter mice or novel genetic manipulation techniques). For example, what key models were developed in the past year? After the newest and most representative models are identified, the NCI could work with the investigators to ensure that the mice are widely available. Reviewing, documenting, and publicizing key developments in the application of mouse models to cancer research—including developments that changed the treatment of cancer—is critical.

#### **Education**

In general, more education is needed about the research applications for mouse models; education about the value of GEMMs in translational research can increase acceptance of using mouse models. Researchers should have more opportunities to become aware of the clinical applications of their work. Scientists must use the best models for the disease being studied. Education also could increase the willingness of scientists to accept new technology.

### **Training**

Education and training in animal experiments should be prioritized to improve reproducibility and help researchers transition to working with mouse models. For example, many investigators have a poor understanding of animal behavior and would benefit from education in this arena, and training is needed for vivarium staff to know how to properly dose animals 7 days a week for preclinical studies. Training and information should help investigators address the limitations of mouse models, as well as more easily and accurately interpret findings from the models. Young investigators should be trained in multiple disciplines: A fellowship or postdoctoral training program could be helpful, as would meetings and workshops. Notably, for those investigators who do not have time to train research team members, collaborations are very important. Several specific topics emerged as priorities for training:

- Comparative pathology
- Molecular epidemiology
- Pharmacology
- Genomics
- Statistical analysis
- Study design
- New models and technology
- Animal procedures
- Animal behavior
- Modeling epidemiologic exposures
- Quantitative and population genetics
- Disease-specific expertise

### **Meetings and Workshops**

Stakeholders referred to meetings and workshops in many different contexts. For example, workshops would be useful to address the need for more education within the community about mouse model resources and how best to use them. Sessions at national meetings could include speakers from multiple disciplines that use mouse models or information generated by mouse models. Speaking about the same disease condition from various perspectives helps scientists understand and pay attention to different forms of research. Better awareness of which groups are focusing on which tumor types with which models could be fostered through conferences. Stakeholders also suggested holding conferences or workshops to educate the modeling community about the best models to use for studying particular organs or diseases, with the acknowledgement that cross-field fertilization also could be useful. There should be open discussions about what topics are valid to study in mouse models and which are better approached using primary human tissue or human trials.

Disease-centered meetings would be helpful to learn about all mouse models relevant to a specific disease and could facilitate the formation of collaborations. Investigators should be encouraged to form collaborations centered on a specific disease. The NCI and the cancer research community could promote increased participation and awareness of mouse modeling through existing or expanded workshops (e.g., American Association for Cancer Research [AACR] workshops). Conferences could focus on specific pathways or topics of cancer to discuss treatment, diagnosis, prognosis, and translational application of mouse models. Key scientific meetings also could be used to conduct workshops on specific topics, such as best practices for data analysis or humanized mouse models. Many large meetings, such as the AACR, draw key stakeholders who are very influential.

### **Mouse Model Availability and Selection**

Cancer researchers repeatedly cited the need to define the best models to recapitulate human disease. Mouse models need to be characterized, deployed, and made available in a way that is most useful to the community. Information distribution is an important consideration in the cancer research community. Related to the issue of model improvement is the importance of selecting the best model to answer the research question. Shared access to tumors, standard operating procedures (SOPs), and “omics” data was cited as critical to facilitating hypothesis-driven science. Many experts expressed a desire to share their data, reagents, models, and other resources.

### **Challenges**

One challenge facing the community is the use of inappropriate methods and models in mouse studies. For example, many investigators still use cell-line xenografts, when a PDX would be more appropriate. Also, many drugs are not tested in the appropriate organ in animal studies. Investigators involved in animal studies may be focused on using models and methods that rapidly produce positive results (under publication pressure), even if they may not be appropriate for translation to human treatments. Understanding which models are available for any particular therapeutic indication is important.

Centralized databases are clearly needed, in particular, a curated database of validated mouse models that would help investigators determine which models are the best to use for their specific question. Many investigators noted that there is no systematic way to know what models are available and where to find them. This makes it difficult to collaborate and make the best use of available resources. Currently, GEMMs with no phenotype are not published, and research is being replicated because of the deficiency.

Accessibility to interesting and useful models is a challenge. The lack of centralized strain repositories and distribution processes results in a barrier for researchers, who often do not know what models are available and spend valuable resources to recreate existing models. There have been several attempts to develop a platform to share models effectively, but cost is a large factor, and sharing mice across facilities is complicated by the poor health status of some strains.

Information and data sharing is a big challenge within the cancer research community. Interviewees both appreciated the logistical challenges and emphasized the importance of developing mechanisms to facilitate sharing mouse models and data.

### **Opportunities**

Stakeholder suggestions related to mouse model availability and selection fell into three broad categories:

- Mouse Model Databases
- Mouse Model Repositories
- Mouse Model Selection

#### ***Mouse Model Databases***

Selecting the right model can shorten time to the clinic, and an online system for exchanging information would accelerate this progress. Generating a database for data on mouse models would help to promote data sharing and avoid duplication of efforts. The interviewees agreed that mouse model data should be made publicly available. The benefits of sharing data outweigh the risks of losing a competitive advantage, according to many stakeholders. The database also could provide information about preclinical trials, formatted similarly to [clinicaltrials.gov](http://clinicaltrials.gov), so that data from preclinical studies can be made available to clinicians.

A mouse model database should provide a central place to organize standardized information about the model phenotypes, histology, and so forth, to enable available information about the different models to

be integrated in a useful way. Communicating about what models exist—especially with the advent of CRISPR technology, which allows much faster generation of models—will be important to keep researchers informed of the availability of new models. As an example, The Mouse Tumor Biology Database (developed by Jackson Laboratories) creates an integrated community information resource to support the use of mice in cancer research. One principle is to integrate data from several different sites into one convenient platform. As another example, AstraZeneca uses in-house software called PREDICT as a single source for all *in vivo* efficacy and pharmacokinetic/pharmacodynamics (PK/PD) data at the individual model level. PREDICT encompasses all models, including GEMMs and xenograft models. A mouse tumor genomics database would be a huge advantage to query the genetics of any model to select the best fit for the particular research application.

A database could provide information about reliable models of specific diseases, along with omics, imaging, and bioinformatics characteristics. Specific elements of the mouse model database suggested by researchers include:

- Available mouse models
- Source of the model (who has them, academic or private)
- Genetic background
- Sequencing data
- Molecular annotation (indels, mutations, copy number variations)
- Gene expression data
- Phenotype information
  - Percentage of mice that developed tumors by a specific age
  - Tumor development characteristics
  - GEMM breeding information
  - Behavior
- Histology
- Pharmacodynamics
- Toxicological data
- Preclinical study results
- Information about available murine antibodies and their application
- Model indications

Researchers emphasized that the stability of funding for such a resource would be critical, and keeping the data current and communicating freely is critical. Many stakeholders agreed that including negative data in a database would be a helpful way for investigators to conserve resources by eliminating redundant experiments. A database of negative results would help other researchers avoid pitfalls. As an incentive to include all data in a public community database, several investigators suggested imposing a requirement for publication that investigators deposit data into shared databases.

### ***Mouse Model Repositories***

A majority of investigators noted that a commercial mouse repository or stock center would facilitate the sharing of appropriate strains of mice, serving to accelerate the pace of research and discovery. A centralized, national facility would help investigators choose relevant models, ensure availability, and allow faster distribution of models. Models for such a centralized repository exist in the fly, worm, and zebrafish communities. Shared access to models also will reduce individual costs on investigators. Importantly, investigators must know that the mouse repositories exist to receive the greatest value.

Many researchers specifically expressed the need for the creation of a PDX repository, with public access to PDX models developed by pharmaceutical companies and academic institutions. They see a need for

the NCI to centralize propagation and distribution of PDX models, maintaining a database of model properties. The models within the PDX archive should be characterized with regard to drug sensitivity and genetic profiles. Xenograft lines and associated data should be curated and reviewed for quality. The full genomic characterization could be available in a portal, and one dedicated research group could perform all profiling to ensure that the results are comparable.

One investigator cautioned that centralized tumor banks might not be the best model. For example, many mice are too ill to be shipped, transporting mice between institutions may result in a long quarantine period that delays research, and the stress of shipping might influence the disease course in the mouse. Providing information about model availability in a database (similar to the NCI's Virtual Tissue Repository) or curating a list of willing collaborators would help to foster partnerships.

Several investigators suggested creating a validated group of labeled, standardized cell lines available from a central entity to facilitate research; this database could be modeled after the Cancer Cell Line Encyclopedia, which characterized cell lines and made them available to the public. Each cell line is SNP profiled with a genomic fingerprint. Similarly, a systematic platform of tools for developing new mouse models would help with comparability between studies. For example, scientists could engineer conditional mice to create a uniform platform of cell type-specific promoters, which could be made available through the repository. The NCI could also create a central resource for sharing experimental reagents, such as antibodies.

### **Mouse Model Selection**

Together, mouse model databases and repositories can facilitate model selection through an improved understanding of which strains are best for which applications. These mechanisms should help to make the community more aware of which models are most suitable for specific research questions or diseases. An integrated map of publications, available models, and where to obtain these models could help researchers form collaborations. Selecting the best model for a particular application requires an awareness of the background mouse genes or other factors that could influence the experiment.

Testing of different models for translational use and the dissemination of results could be facilitated through conferences or workshops focusing on tools and models in cancer research.

### **Core Facilities**

Centralizing experience and expertise in developed infrastructure, such as shared facilities and laboratory cores, would allow clinical and basic researchers to work together on important questions.

### **Challenges**

Breeding and expanding mouse models is laborious, time consuming, and expensive. Mouse studies require expensive infrastructure for animal husbandry, as well as specialized instrumentation for experimental and other analyses. Many investigators mentioned the barrier of access to expertise in core facilities. Although many universities have core facilities for sequencing and microscopy, there is a paucity of centralized mouse facilities in many academic institutions. Several researchers also commented on the need for access to bioinformatics expertise and tools, as well as pathology expertise. Although some institutions subsidize mouse costs, many cannot afford to do so. The NCI could help with expertise by lending services or through a database that points investigators in the direction of resources.

Normally, immediate translation and application of laboratory results in patient treatment is done in specialized cancer or academic research institutes. Infrastructure issues, such as proximity of hospitals and specialized laboratories, currently do not permit this type of rapid access.

## **Opportunities**

Funding for mouse and technical expertise core facilities would help address concerns with expertise availability and standardization.

### **Mouse Cores**

Financial efficiency could be gained with an institution-wide mouse core facility, which would also encourage researchers without mouse experience to embark on new studies. One investigator detailed the collaborative environment of his institution, which runs a mouse core facility. Investigators come to the core to solicit advice on how to create the models, and then return to better understand the phenotypes and what those phenotypes mean. Institutions need to develop their capacity for PDX—it is necessary to get the tumor from the patient into the mouse quickly, which requires a well-trained, highly skilled team, including an experienced surgeon. Several cancer researchers suggested the need for a “mouse hospital” or facility with drug dosing and imaging technologies that would allow studies of tumor progression over time. One example cited by several researchers is the mouse hospital at Memorial Sloan Kettering.

### **Technical Expertise Cores**

Interviewees mentioned a need for bioinformatics, imaging, and assay core facilities. Analyses of statistical power and study design could be provided by in-house statisticians in core facilities, and support for core imaging facilities would help to address the challenge of expensive imaging instrumentation. Using core laboratories to perform drug screening would help advance mouse model research and would be more efficient. In one possible model, academia would conceive of experiments to be carried out by the NIH or Contract Research Organizations (CROs). Dedicated and knowledgeable technical support would run the assays and ensure that experiments are conducted and analyzed properly. This method would facilitate comparisons between compounds by ensuring consistency across the experiments. This type of consultant service would be particularly helpful for epidemiologists, who do not have the training to conduct mouse experiments. Another idea is for NCI Cancer Centers to provide core facilities for animal models, including training.

## **Pathology**

Comparative pathologists, who have experience in both human and mouse pathology, are critical for interpreting data from mouse experiments and comparing those results to the human situation.

## **Challenges**

There is a shortage of well-trained veterinary and comparative pathologists, and not many young investigators are being trained in this area. Institutions lack funding and support to train pathologists. This raises concern because too many errors in pathology are produced by untrained personnel. Scientists can become reasonably good at interpreting pathology, but unexpected properties or an unanticipated phenotype in a different tissue would be noticed only by a trained pathologist with broad expertise. Many respondents indicated that pathology is underappreciated. Often, pathologists are not acknowledged (or consulted) in mouse publications.

## **Opportunities**

Pathology is important in characterizing models, and every mouse model should be analyzed by trained pathologists. It is important for trained scientists to compare development, cancer emergence, and tumor progression. Pathology images related to a study should be made available to the community and deposited in a database upon publication, similar to sequencing or gene expression data. Several investigators mentioned that having a centralized pathology core available at academic institutions to

analyze markers carefully would be helpful. There should be more input from pathologists when the models are being developed to ensure that what is being tested is applicable to the human condition.

The mouse pathologist is a critical component of the translational research team, and more individuals need to be trained to support the research project. A specific community of practice of pathologists was suggested for professionals to share their expertise. At national pathology conventions, pathologists could learn to handle mouse tissue. One model for collaboration could be to put a pathologist as a percentage of a grant. Another stakeholder mentioned that the NCI should recognize the contributions of veterinarian pathologists to biomedical research.

## **Standardization and Best Practices**

The research community voiced strong support for the standardization of protocols and data and the development of guidance for the use of mouse models in cancer research.

### **Challenges**

Data and process standardization arose as high-priority issues for many researchers. The lack of data standardization makes it difficult for scientists to interpret animal model data. Researchers noted the lack of SOPs for common procedures, such as xenograft transplantation. Standardization would ensure better reproducibility between experiments.

Comparability of results between laboratories is a concern. For example, smaller companies often lack a vivarium, and mouse experiments are outsourced to academic laboratories or CROs. There is often a wide disparity in timelines and data quality, depending on the laboratory, and the company has little control over the study design and data quality.

Many published preclinical studies define success by response, not survival, which results in high failure rates in clinical studies. Experimental therapeutics are moved too quickly to clinical studies based on incorrect endpoints. Endpoints used in preclinical trials are often different from those that are used in human studies. For example, many preclinical experiments measure only whether a tumor decreased in size. Relevant outcomes must be studied in mice—neurofibromatosis, for example, often affects the visual pathway in children; there is a need to investigate the effects on visual pathways in mice.

Data harmonization requires significant technical support; the community would benefit from a common format to access standardized data. Standardization of experimental approaches is critically important. PDX modelers use many different methods to implant the xenograft (e.g., a humanized mammary fat pad versus a mammary gland). Funds are needed to test these methods and determine the best protocols for imaging and other techniques.

### **Opportunities**

Standardization of data is key to ensuring comparability of data sets and correct interpretation of results. For example, collecting data in a standardized way would enable the pooling of data sets and facilitate comparisons of study results, thereby increasing the statistical power of studies and improving scientists' ability to answer questions. Standardization should include not only characterization but also data collection, storage, and dissemination. Stakeholders called for the standardization of—

- Pathology data
- Imaging data
- Preclinical endpoints
- Staging of mouse tumors

- Genetic/genomic/proteomic characterization

The cancer research community should collaboratively identify, develop, and share best practices. SOPs should be made publicly available to increase consistency across studies and allow data sets to be combined. The need for specific SOPs/best practices in the use of mouse models in cancer research was mentioned for several areas:

- Quality control processes: Consistency and quality control are critical to ensure that studies of compounds in mouse models are translatable to the clinic.
- Mouse husbandry: Standardized mouse handling, including the mouse housing environment, would promote experimental reproducibility.
- Drug testing guidelines: The community needs a standardized framework for testing drugs in preclinical trials, including guidelines that identify which models best recapitulate human disease. Teams of multidisciplinary researchers who study each particular organ system could be tasked with creating the guidelines.
- Best practices for PDX: The community would benefit from SOPs regarding model maintenance to prevent drift.
- Tumor growth: The NCI could develop a “gold standard” on how to interpret tumor growth following therapeutic treatment. For example, the guidance could specify that tumor growth be calculated in a particular way for publications and grants. The definition of statistical and biological significance should be clearly articulated through guidelines; varying definitions of significance often lead to disparate findings.
- Data analysis: Data analysis standards of practice will increase confidence in published figures. Best practices (particularly for statistical analyses) for publishing and sharing with the wider community would be helpful.
- Preclinical measurements: The NCI could encourage that mouse models use the same preclinical measurements as those used in human trials to standardize and reflect clinically meaningful endpoints. The metabolic and pharmacokinetic data collected in mice need to be similar to the data collected in human trials. Some NCI groups, such as the Children’s Oncology Group (COG), are defining mouse endpoints to be consistent with human trials.
- Treatment decisions: Guidelines for using models in treatment decisions was identified as a community need.
- Publication requirements: The NCI and peer-reviewed journals should require more detailed information about mouse models used in studies, including descriptions of such basic information as the age and sex of the animals studied. The NIH could release guidelines about the information that needs to appear in publications. Many papers report differences in tumor size between treated and untreated groups, but often the tumor is still growing in the treated groups. Incorrect interpretations often result in failed clinical assessments. The bar needs to be raised on what findings can be published as efficacious.
- Guidelines for academic-private partnerships: Sharing best practices, such as a legal framework or financial relationship that has worked in a particular situation, would be helpful to share with others to foster partnerships.

## Funding

The generation of GEMMs and other models requires unique skills and takes more time than other experiments. Interviewees universally acknowledged that funding is inadequate for mouse model projects. Along with insufficient funding, the long time period required to conduct mouse model experiments was mentioned frequently as a barrier to conducting translational mouse experiments. Also, mouse experiment-related technology, such as imaging tools, is expensive.



## **Challenges**

The main limitation to mouse studies, cited by many interviewees, is limited funding. Many outstanding grants are not getting funded. The cost of mouse husbandry and vivarium infrastructure (e.g., housing, breeding, maintaining mice) is increasing, and it is expensive to sustain the multiple genetic strains of mice necessary for translational research. Insufficient funding results in using fewer mice for experiments, which reduces the statistical power of the results and limits the conclusions that can be drawn from the data. As funding levels decrease, the number of investigators also decreases, which is a big concern. New assistant professors are leaving the field because of the difficulty in securing funding without an established research record. Several stakeholders emphasized the need to fund young investigators to maintain an influx of talent to the field.

The expensive and time-consuming nature of mouse projects does not translate well to study sections. Many investigators took issue with grant review panels for not recognizing and appreciating the value in mouse model research. Panelists were described as “not very open-minded.” Given the long time scale needed to conduct mouse studies, expected publication rates are unrealistic for mouse model research. In addition to the unrealistic expectations for publication rates, reviewers occasionally suggest costly experiments that would not raise the visibility of a manuscript (e.g., testing additional doses), which was considered a drawback by some investigators. Several investigators noted that combined approaches, such as integrated human and mouse experiments, also do not score well in study sections. The amount of oversight for animal protocols required for grant applications is onerous. Streamlining the process would lessen the investigator’s burden.

Currently, no funding mechanism supports translational work, such as taking patient samples from the operating room and bringing them into the laboratory to transplant into a mouse. New funding mechanisms are needed to improve translation of work with mouse models to human treatments. Furthermore, many mouse studies that include screens or microarrays are not considered “hypothesis-driven” and thus are not funded. R01 grants are focused on testing hypotheses, and there is a need for foundational, exploratory, descriptive research funding. Funding for the development of mouse models also is difficult to obtain. Funding usually becomes readily available only after a model has been developed and preliminary data of its efficacy have been generated (which usually takes a couple of years). The development and testing process alone is very expensive, so new funding mechanisms need to cover these activities (or they need to be included as part of larger studies) and to provide support prior to the development of models.

In addition to the expense of developing novel models, it is difficult logistically to adopt new models. Scientists should be encouraged to adopt new technology and models.

## **Opportunities**

Stakeholders professed overwhelming support for NCI’s continued investment in mouse modeling research.

Scientists called for research budgets to be expanded, either through supplements to existing funding sources or new funding mechanisms. Different grants and awards are needed for translational research to advance novel therapies. Many specific funding priorities were suggested by the interviewees, including those below:

### ***Opportunities to Encourage Collaboration***

- Support the formation of multidisciplinary research teams.
- Support collaborations between basic science and clinical researchers.

- Develop a funding criterion to require both basic and clinical Principal Investigators on a grant.
- Create incentives for basic researchers to interact with clinicians.
- Support local interactions between basic scientists and clinicians at the same institution.
- Support academic-private partnerships.
  - Provide matching funds to encourage pharmaceutical companies to collaborate with academic laboratories.
  - Create and fund a platform to share pharmaceutical drugs with academic researchers.
  - Use the Small Business Innovation Research model to support interaction and collaboration between academic researchers and pharmaceutical companies.

### **Opportunities to Address Research Priorities**

- Develop specific funding mechanisms for mouse modelers, taking into account the long time and expense of building new models.
- Prioritize 5-year grants over 3-year grants for mouse research.
- Develop a funding mechanism for exploratory research.
  - Seed grants or an R21 mechanism would generate useful, translatable information.
- Provide more funding for the High Risk–High Rewards program.
- Provide a mechanism for new investigators to collect preliminary data.
- Develop a small granting system to cover costs of distributing models.
- Create a funding mechanism for cancer pathology.
- Support model qualification.
- Fund co-clinical trials.
- Release training grants for molecular epidemiology in animal and human models.
- Develop funding for paired research to foster partnerships between human and animal model projects.

Scientists on grant review panels should be educated about the benefits of mouse model research, including the recognition that the right model depends on the question being asked. Reviewers need sufficient skills in basic, clinical, and observational research. Study sections should include researchers who work with mice to ensure that the panel considers the time and costs involved in using mouse models for preclinical studies. Also, grant reviewers should adjust their expectations for publication rates for mouse projects.

Cancer researchers often receive funding from private foundations. Creative mechanisms, such as grants that match private investment in translational studies (e.g., University of California Discovery Awards), should be pursued. Public-private partnerships might offer an opportunity to fund the development of mouse models.

### **Technology Transfer and Data Sharing**

Many researchers across the spectrum of academia and the private sector mentioned the difficulty in gaining access to the best mouse models and relevant data. Improving technology transfer and data sharing agreements for universities and companies is a high priority for the cancer research stakeholders.

### **Challenges**

Some investigators are reluctant to make their mouse models available for validation or other experiments. Although the majority of stakeholders interviewed favored the sharing of data, models, and

resources, many noted a pervasive reluctance or outright refusal to share among some investigators within the modeling community.

Many of the academic researchers identified access to pharmaceutical compounds as a major barrier to research. Licensing, publishing restrictions, and intellectual property (IP) rights are all obstacles to collaboration. It is difficult to license models, especially for multi-allelic mice. One academic researcher noted that establishing a partnership with a pharmaceutical company required extensive negotiation to solve issues related to patents, publications, confidentiality, and so forth. There is a need for more open, reciprocal transfer of information between the two sectors. The time frame to negotiate agreements, such as material transfer agreements (MTAs), with pharmaceutical companies to obtain drugs is too long—it can take months. Pharmaceutical companies hesitate to test combinations of drugs because adverse effects reflect poorly on every drug in the combination. IP and reporting issues must be resolved so that combinations of drugs can be tested.

### **Opportunities**

One suggestion, mentioned several times, was for the NCI to create a framework to facilitate access to drugs and antibodies. Ideally, these materials would be placed in the public domain for easier access. Specifically, the NCI could arrange for companies to provide a kilogram of a drug, such as a MEK inhibitor, to the NCI, which would distribute the drug as needed. The general sentiment was that it would be valuable for the NCI to work with industry and academia to develop collaboration terms that are reasonable for both parties involved. The NCI could facilitate addressing the IP issues and perhaps create a clearinghouse to expedite access to drugs for testing. Guarantees of protection from competitors could encourage data sharing by private sector companies.

The NCI also could help remove some of the IP obstacles to collaborations. Several investigators mentioned the utility of sharing guidelines and best practices for these types of collaborations. It currently can take months for companies to negotiate an MTA. The NIH's licensing group could develop a template for a universal MTA. The NIH also could make the process easier through bundling licenses or providing access across multiple models to facilitate adoption. If the NIH can broker agreements faster, it could fundamentally change how science is performed.

Translational research would also benefit from rapid access to new agents developed at pharmaceutical companies. The NCI has made some drugs available (e.g., through the Cancer Therapy Evaluation Program [CTEP]); several investigators suggested expanding CTEP to allow researchers to access a wider range of drugs. Data from preclinical studies should be made available to clinicians.

Funding mechanisms can be structured to require that mouse models and data be available to other investigators. The data should be made available at the time the mouse is deposited. If studies are funded by the NIH, those models should be made available without exorbitant costs. Some laboratories derive a cancer cell line model and charge as much as \$100,000 for it. This is a significant barrier to drug discovery and developing therapies that benefit patients.

## *IV. Development of Tools and Techniques*

Many issues related to the development of mouse models (e.g., lengthy development process, lack of representativeness) can be addressed with improved technology. Cancer research stakeholders emphasized the need to develop new tools—such as imaging technology, bioinformatics programs, and gene editing processes—to facilitate translational mouse research. Several investigators voiced concern that some researchers tend to prefer old approaches rather than adopt new technology. Improved technology can address specific issues, including the following:

- Lengthy time to build new models
- Inadequate noninvasive imaging of tumor growth
- Data analysis

The cancer research community stakeholders contributed many helpful suggestions regarding priorities for the development of tools and techniques. The suggestions were categorized into the following themes:

- Experimental Techniques
- Study Design
- Bioinformatics and Statistics

### **Experimental Techniques**

This field of science is constantly evolving, and new tools and techniques are always being developed. New technology, for example, allows for the rapid generation and testing of models that reflect any particular human aberration. Cancer research stakeholders mentioned that the field would benefit from certain improvements, such as the development of high-resolution, noninvasive imaging techniques to facilitate the use of mouse models in translational research.

#### **Challenges**

Current imaging technologies are often invasive, requiring the sacrifice of mice at various time points in the development of a tumor, requiring the use of many additional mice for each research project.

With traditional gene-editing techniques, the development of novel GEMMs is laborious and expensive. Reducing the duration from model concept to completion would significantly increase resources available for conducting experiments.

New technology is needed to monitor the effect of drugs on tumors. Currently, tumor volume is measured by caliper, a crude type of measurement.

#### **Opportunities**

Cancer researchers suggested focusing on several experimental techniques to advance the science. Some of these are described below.

#### **Imaging**

Full-body noninvasive imaging techniques present emerging opportunities for the study of human disease and mice. These new techniques will allow researchers to keep the mouse alive during the development of cancer and perform imaging at various intervals. The development of imaging strategies for use in clinical settings also can be addressed using mouse models, as mice provide a platform for testing new imaging modalities (e.g., metastasis imaging). Mice can provide robust readouts of signaling pathway activity. Although this information could be obtained through sequencing, imaging techniques are better than biopsies because they are less invasive. Imaging techniques with single-cell resolution will facilitate observation. Imaging methods that use bioluminescent and fluorescent reporters should be pursued as well.

#### **Rapid Gene Editing Techniques**

CRISPR was mentioned often as an emerging opportunity to build precise models in a much shorter time frame than was previously possible. This method, allows more rapid introduction of genetic mutations or deletions into mice, is revolutionizing the use of mouse genetics to address biological and disease

questions and making models more translatable to the human setting. Using CRISPR to develop GEMMs provides the opportunity for better and faster functional characterization of oncogenes. Other models, such as the *sleeping beauty* model of mutagenesis, represent additional opportunities.

### **Sequencing**

Both academic and private sector researchers rely on sequencing data to understand the genetic basis for disease, monitor changes during tumor evolution, and compare experimental results. Full genome sequencing, RNA profiling, and proteomics analysis can help illuminate the genetic nature of tumor progression. These techniques, however, are expensive, and the analysis is not trivial. The techniques should be made more widely available.

### **High-Throughput Techniques**

High-throughput analysis of mouse model experiments presents another opportunity. Multiplexing *in vivo* pharmacology studies should be designed so that mice can be used to test different drugs. Similarly, high-throughput techniques, such as drug screening platforms, should be developed to allow faster evaluation of compounds in an *in vivo* setting. There is a need for more rapid and economical screening technologies to determine which drugs or combination of drugs are most likely to be effective.

### **Secondary Reagent Generation**

A researcher suggested generating secondary reagents from human specimens. For example, when the tumor is removed for biopsy, monocytes can be collected and immortalized to create matched cell lines and xenograft. These resources can be used to determine if a mutation is unique to the tumor or germline.

### **Cell Purification**

Purification of tumor cells is more easily accomplished in mice, which can exploit the use of reporter alleles. New imaging technologies, such as fluorescence-activated cell sorting (FACS) and CyTOF mass cytometers, should be adopted widely. Scientists also mentioned applying single-cell technology and proteomics to mouse model studies.

### **Implantation and Dosing**

An investigator suggested the need to develop techniques to increase the rate at which tumors are successfully implanted into the mice (“take rate”). Another scientist noted that intravenous dosing is challenging and time-consuming; better techniques are needed for dosing, especially for cutting-edge biologics and RNA/DNA treatments.

### **Study Design**

A robust mouse study design is critical for ensuring reproducible, relevant results that translate to the clinic. Many stakeholders commented on the use of mouse models to inform clinical protocols.

### **Challenges**

Mouse experiments tend to be time consuming and costly. Current studies are limited by time and money, and it would be useful if mice could be reused to test different drugs. *In vitro* screening is high-throughput, but produces many false positives. The next challenge is to develop an *in vivo* screen to reliably and quickly assess efficacy.

A simple measure of tumor size is not very useful without showing dose-response. The timeline for preclinical pharmacology studies is not aligned with human clinical trials. Often, clinicians will decide to take a compound to clinical trials before the mouse preclinical trial is completed.

In humans, it can take decades for an exposure to result in a tumor. One challenge is to develop technology and study designs that accelerate the effects of an exposure on tissues for modeling epidemiological risk factors in mice.

### **Opportunities**

Improved study design, such as blinding with an outside pathologist, can ensure robust results. Several specific areas warranting additional consideration in study design are described below.

#### **Multiple Models**

Many investigators noted the importance of using more than one model—such as GEMM and PDX models—side-by-side in a study to add confidence to the results. Ideally, investigators use several different strains to see how specific genes affect the development of cancer. One investigator mentioned that both GEMM and PDX models are essential, as there are not enough human tissue samples to justify human experiments. A combination approach would use syngeneic models, as well as PDX and *in vitro* experiments, to increase confidence in the experimental results.

#### **Preclinical and Clinical Integration**

Collaborations between basic or translational scientists, clinicians, and pathologists would ensure that mouse work is relevant to the clinic. Using information from studies of signaling pathways in mice can help to design better clinical trials. The NCI could provide an opportunity for preclinical researchers to ask clinicians what models should be developed; such dialogue has been informative in the past. Preclinical tests in mice allow clinicians to design better human clinical trials, and preclinical animal data can strengthen the rationale for starting a clinical trial. Furthermore, investigators recommended that clinical trials be required to have more extensive preclinical data before human studies begin.

#### **Co-Clinical Trials**

Co-clinical trials, in which a drug is tested simultaneously in mice and humans, is a good method to study the progression of disease and understand implications of treatment. Integration of mouse and human experiments is critical to compare bioinformatics, signaling pathways, and so forth to determine if the mouse mimics response to treatment. Co-clinical trials allow the mouse data to lend very quick insights into genetically defined patient subgroups, such as treatment responders and nonresponders. Mouse data then can be used to inform the clinical treatment choice based on the molecular characteristics of the tumor. One investigator, however, opined that co-clinical trials are not useful, and mouse data should precede human studies.

#### **Diversity**

A challenge is the lack of gender diversity in mouse studies. Female mice are easier to house, but are not representative of the human population. Mouse studies can be leveraged to investigate gender- and age-specific responses to cancer treatment. There is also a need to study exposure at a variety of ages.

#### **Bi-Directional Studies**

Studies should be designed as a bidirectional pipeline. Translation is not just from the bench to the clinic, but also from the clinic back to the bench. Sometimes, clinical observations need to be studied in the laboratory. Another exciting opportunity is to take clues from epidemiologic association studies and use them in models. These studies can go from the human to the mouse, but scientists also can use the genes identified in mouse models and associate them with cancer predisposition for human studies. One avenue for integration between epidemiologic and mouse studies is response to treatment according to the specificity of tumor types. It is important to test epidemiological questions in models that are meaningful in a clinical situation or for their relevance to public health.

### **Study of Refractory Disease**

Another limitation is that many models are used to test naïve disease rather than refractory disease. Currently, most drugs are tested on mice that have not undergone chemotherapy or radiation. In contrast, patients in human trials often have been treated previously with chemotherapy or radiation, which affects the drug response. Mice in preclinical studies need to be treated in way similar to humans in clinical trials to make the results more comparable between the two systems. If an investigator is interested in the use of a drug in liver metastasis, then that drug should be tested in a mouse scenario where liver cancer was treated and the cells metastasized. Mice could also be treated with chemotherapy and radiation before entering a preclinical trial to simulate the conditions in human trials.

### **Exposure Studies**

Methodology should be developed to address exposure to carcinogens and mixed exposure to mimic the human experience. The research community needs good systems for exposing mice to environmental risk factors to determine how external exposures drive cancer.

### **Bioinformatics and Statistics**

Many interviewees condoned the importance of improved bioinformatics and statistical analysis for improved experimental design and resulting data analysis. Bioinformatics is often applied to understand the relevance of mouse results to human disease.

### **Challenges**

Interviewees acknowledged that bioinformatics tools are insufficiently developed to analyze data from mouse preclinical trials. Using bioinformatics tools to integrate omics data (e.g., genomic, transcriptomic, metabolomic, proteomic) can help determine activated pathways in tumors, determine the response of a pathway to treatments, and gain a comprehensive understanding of tumors. Analysis of sequencing data also is complicated.

Many molecular biologists have not been adequately trained in statistics and lack expertise in experimental design and computational modeling. Computational analysis can facilitate studies designed to allow multiple variables. Inadequate statistics affect the interpretation of many study findings.

In many settings, mouse models are not used appropriately because the studies are insufficiently powered and are not designed to test PK/PD relationships. Preclinical studies should be planned with consideration of statistics and power implications.

### **Opportunities**

Computational biology and informatics tools should be developed and made accessible to bench scientists. Computational methods and flow cytometry technology, for example, can be used to understand how cells within a tumor interact with each other. An opportunity exists to develop novel mathematical models to account for the effects of genes on disease risk and other complex phenotypes. Simulation modeling can be used to understand the impact of multiple risk factors in cancer etiology. Biostatisticians who are familiar with both mouse and human data should be included as an integral part of project teams.

Sophisticated, statistically savvy designs are needed to model a diversity of mechanisms and effects in mice. Design trial and power size need to be applied more effectively in the preclinical space. Statistical methods, for example, should be developed to determine accurately how many mice are needed to produce statistically significant results. Projects need to plan for and incorporate sophisticated statistical

methods, such as ANOVA, into data interpretation. Scientists should ensure that the statistical rigor of clinical trials is applied to preclinical mouse studies.

## *V. Collaborations*

A major theme arising from the interviews was the need to foster partnerships between various research sectors, disciplines, and topics. Stakeholders urged more support for collaborations, both across stakeholder groups (academic, private sector, public institutions) and across disciplines (basic, clinical).

Many stakeholders acknowledged that the NCI already encourages collaborations, but noted that more can be done. Stakeholder suggestions were relevant to the following types of collaborations:

- Public-Private Partnerships
- Academic-Private Partnerships
- Public-Academic Partnerships
- Private Sector Partnerships
- Multidisciplinary Team Integration

### **Public-Private Partnerships**

Public-private partnerships were defined as relationships between the private sector and government institutions.

#### **Challenges**

Data sharing was identified as a significant barrier to translational research, and the creation of public-private partnerships is one way to address this need is an important priority. More engagement is needed from both the NIH and FDA to support mouse preclinical research.

#### **Opportunities**

Industry stakeholders welcomed NIH collaborations and support. Many cancer researchers acknowledged the need for grants to support public-private partnerships. Several mechanisms for sharing data were proposed by the participants. The NCI could support large-scale studies of the types of tumors likely to be sensitive to specific drugs supplied by pharmaceutical companies; this would ensure experimental consistency and comparability across studies.

One stakeholder suggested that the NCI support major cancer issues and that private foundations or insurance companies support rare cancer research. Insurance companies should support cancer research because of their vested interest in reducing the large costs incurred by cancer patients. Patient advocacy groups and the NCI could provide funds for shared resources that benefit public-private partnerships.

Stakeholders mentioned the need for collaborations between the NIH and major mouse providers, such as Jackson Laboratories. The NCI could moderate third-party experiments; industry could pay to conduct the study at a government facility.

Stakeholders proposed better use of Federal science advisory boards and consultants to provide advice on moving drugs from mouse to human experiments in the translational phase.



## Academic-Private Partnerships

Creating an interface for collaboration between industry and academia was a high-priority request from many interviewees. Industry provides reagents to academics, and academic researchers provide expertise to industry, such as advice on the best models or access to the models. Pharmaceutical companies would benefit from working with academic researchers, but they are often not open to collaboration due to IP and patent issues. Many stakeholders described mutually beneficial partnerships between industry and academia.

### Challenges

Generally, the infrastructure is lacking to facilitate effective collaborations between academia and industry. Financial and IP issues also complicate collaborations with industry. Drug companies produce therapeutics or antibodies that researchers cannot access due to IP concerns, often resulting in the academic investigators' needing to synthesize the drug themselves, which is both costly and time consuming. Sometimes, pharmaceutical companies do not allow investigators to publish data.

### Opportunities

Collaborations between academia and industry can be leveraged to translate compounds to the clinic. Sometimes, a chemist has a compound and creates a company, but that creates a large translational gap. Partnerships between industry and academia can address this gap. Industry could provide the materials, therapeutics, genomic data, and perspectives, while academia provides the reagents, techniques, expertise, and fresh ideas. Pharmaceutical companies also can perform the pharmacokinetic and pharmacodynamic analyses.

Close interactions between investigators from academia and the private sector also will ensure that basic researchers produce preclinical data that meet industry standards, which can be helpful in securing MTAs and moving research findings to clinical trials. Researchers would benefit from greater access to information about drug properties from pharmaceutical companies. Joint academic-private clinics could facilitate preclinical studies. This type of resource can be used to examine the predictability of mouse models.

One participant suggested that the NCI facilitate the use of CROs by academics by providing a funding mechanism to support scientists who would like to use the services of CROs. This would help academic investigators complete toxicology testing and push drugs to phase I clinical trials.

A side benefit of academic-private partnerships is that industry could introduce academics to different career paths.

## Public-Academic Partnerships

Public-academic partnerships were defined as relationships between government institutions and universities or colleges.

### Challenges

The limited funding environment is a challenge for public-academic partnerships. Academic researchers identified the need for dedicated grant mechanisms to support mouse model research.

### Opportunities

Several researchers mentioned the possibility of an NCI-centered facility that could perform experiments for academia. This would facilitate comparisons between experiments and remove some of the funding

pressure from academia. Another suggestion was to integrate the NCI's Specialized Programs of Research Excellence (SPORE) programs with mouse models.

### **Private Sector Partnerships**

Private sector partnerships include relationships between individual companies, including biotechnology companies, pharmaceutical industry, and CROs.

#### **Challenges**

Private sector research often is hampered by the proprietary nature of the various drugs that preclude testing them in combination. Also, many of the larger private sector institutions have their own mouse facilities, but others are too small to support such infrastructure and must collaborate with CROs for preclinical studies.

#### **Opportunities**

In general, the community should be better aligned along private sector, pharmaceutical, biotechnology, and private centers. Several interviewees suggested developing a mechanism to facilitate the use of drug combinations for translational research. For example, a partnership of pharmaceutical companies could use the same PDX model to test multiple drugs. The collaborations must address the companies' concerns about negative reporting to the FDA.

Outsourcing mouse model experiments from pharmaceutical companies to CROs removes the IP concerns. Private companies should build contractual relationships with commercial laboratories and emphasize long-term relationships to facilitate the drug discovery process. This could take the shape of a fee-for-service or risk-sharing agreement where the company is getting paid and also is involved in the discovery and development of the drugs.

Companies could contribute data, such as models and characterization data about the models, to precompetitive consortiums. Information on a specific drug would not be shared prior to publication, but benchmarked data could be disclosed.

### **Multidisciplinary Team Integration**

A large majority of interviewees identified the need to build multidisciplinary teams to improve the use of mouse models in translational research. Infrastructure is needed to coordinate activities between clinicians, translational scientists, and basic researchers.

#### **Challenges**

Several interviewees mentioned the need for a comprehensive approach to mouse model projects and a need to address the culture of working in "silos." There is a disconnect between the laboratories developing innovative mouse models and those that are doing preclinical drug testing; this gap must be closed. Sometimes, cultural differences hinder collaboration. For example, clinical trial physicians are not aware of mouse studies, and mouse researchers do not understand the constraints of clinical research. The barrier and disconnect between the prevention, clinical, and mouse communities needs to be removed, and integrating prevention scientists into the mouse community is a high priority.

Working with people from other disciplines can be challenging because the structure of research studies is different, and training, funding, challenges, and rewards are all different, as is the research vocabulary. Many groups do not have common language between basic, observational, and clinical research; communication across these barriers is important. As with most interdisciplinary research, scientists are

used to working with colleagues in the same field because that is where the resources come from and where the expertise is available and familiar.

Different stakeholder groups have different perspectives and motivations, but all roles are essential. Communication can help to bridge gaps between basic and clinical researchers. One challenge to truly collaborative research teams is the pressure to be a primary author to achieve tenure. Successful collaborations often require equal input from several investigators, and publications need to reflect this.

### **Opportunities**

Researchers across disciplines need to be brought together so that they can learn from each other. There is a strong need to facilitate seamless transdisciplinary communication between those using the models—developing them, refining them, doing translational biology—and the clinical group.

Research teams should be comprised of basic, preclinical, and clinical researchers. Specifically, stakeholders noted that research teams should include clinicians, oncologists, radiologists, geneticists, modelers, systems biologists, pathologists, veterinarians, epidemiologists, and biostatisticians. It is rare to find all skill sets required of translational research in one person, and cross-disciplinary research groups result in better interpretation of data. The inclusion of a variety of expertise and perspectives will ensure that preclinical work is relevant to the clinic. For example, including statisticians and clinicians on research teams helps to guide the research in preparation for clinical trials.

One helpful suggestion is to demonstrate success stories where a multidisciplinary collaboration worked well. These proof-of-principle demonstrations should show that the project creates an impact in both fields. Workshops or discussions to demonstrate proven projects that have worked between mouse modelers and epidemiologists or clinicians would motivate more people to work together.

The NCI could support the formation and activities of translational working groups within institutions. Frequent interactions and meetings are needed to develop and promote transdisciplinary efforts. Because of the cost, incentives may be necessary to encourage participation, especially for new investigators and trainees.

Conversations between clinicians and epidemiologists should be encouraged. The epidemiologist can generate a hypothesis based on observations in human populations that can be tested in the mouse, and mouse modelers can provide human researchers with ideas about which chemicals to study or measure in the blood, urine, or other biospecimens. The NCI could create the setting for cross-disciplinary interaction to discuss how basic research translates to epidemiology, which is not a natural step. Mouse models provide feedback for epidemiologic models in an integrative process.

Many stakeholders identified the need for multidisciplinary research consortia to advance the use of mouse models for translational cancer research. One common suggestion was to create consortia or working groups focused on a disease or organ. These teams could be built with multiple expertise in bioinformatics, immunology, metabolism, and so forth. Funding for disease-specific meetings can encourage collaborations across research disciplines. A consortium could endeavor to prioritize tumor types for the next 5 to 10 years and engage scientists interested in studying those specific tumor types and related medical needs. The consortium could determine the roles of nonprofits, industry, and academia. Data must be shared, and integration of data across institutions is critical. A consortium could develop tools to share information, facilitating the sharing of models and data, encouraging networking, and increasing interactions between basic and clinical researchers. A consortium also could serve as an oversight committee for mouse model research that involves multiple areas of expertise, including mouse modelers (GEMM and PDX experts), clinicians, and basic scientists.

## QUANTITATIVE INTERVIEW ANALYSIS

Although a great number of suggestions for improving the use of mouse models and data generated from mouse models in cancer research were common to all the stakeholder groups, unique themes emerged for each group in the quantitative analysis. Following the interviews, responses were coded according to mention of 36 specific keywords and phrases (Appendix D) distributed across the five categories of *Research Questions and Emerging Opportunities*, *Mouse Model Improvement*, *Cancer Research Community Resources*, *Development of Tools and Techniques*, and *Collaborations*. All responses were tallied and graphed by stakeholder group (Figure 1). Notably, many of the keywords and phrases were distributed somewhat evenly across each stakeholder group. Several differences emerged, which are described in more detail in the individual stakeholder report sections below. The 100 cancer research community stakeholders interviewed identified the following as their top ten priorities:

1. Improving communication and collaboration between researchers (89%).
2. Supporting private-academic partnerships (84%).
3. Characterizing and validating models (67%).
4. Developing a mouse model database (66%).<sup>†</sup>
5. Increasing funding for mouse model research (66%).
6. Focusing on genetics and genomics (59%).
7. Increasing awareness of the importance of mouse model research (52%).<sup>‡</sup>
8. Standardizing methods and analysis (52%).
9. Building humanized mice (52%).
10. Developing improved PDX models (48%).

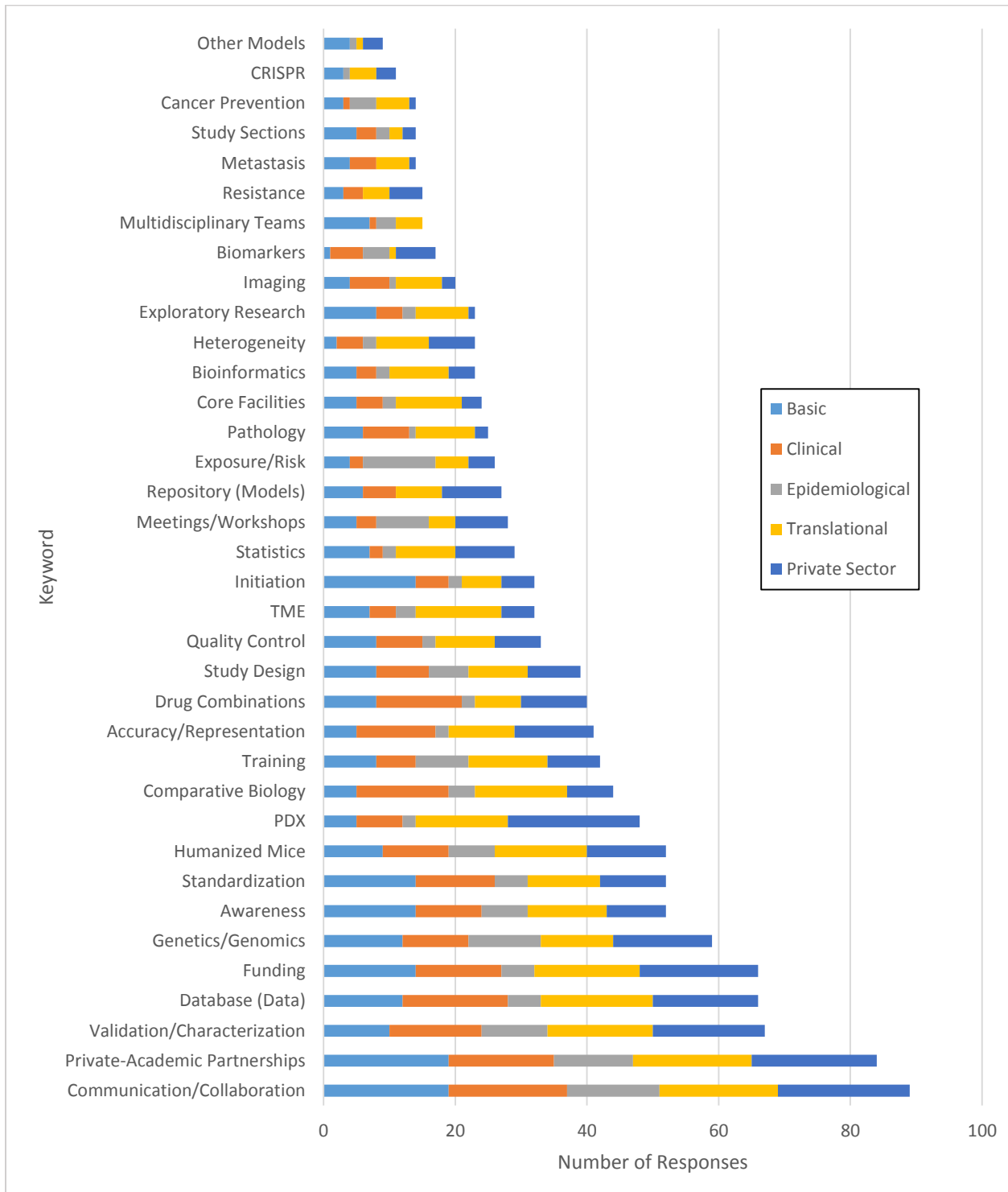
Improving communication and collaboration was the highest priority across all of the stakeholder groups, with 89 percent of the interviewees mentioning this theme. Eighty-four percent of the respondents also specifically mentioned the need to foster private-academic partnerships to leverage the strengths of each group to advance cancer research. Approximately two-thirds of the 100 interviewees supported characterizing and validating models, building a model database, and increasing funding for mouse model research. Focusing on genetics and genomics was the highest priority related to *Research Questions and Emerging Opportunities*, with a response rate of 59 percent. Two additional *Cancer Research Community Resources* themes—increasing awareness and standardization of data and methods—also scored above 50 percent. In the area of *Mouse Model Improvement*, both building humanized mice and improving PDX models were mentioned by about half the interviewees.

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<sup>†</sup> Developing a mouse model database and increasing funding for mouse model research were equally ranked.

<sup>‡</sup> Increasing awareness, standardizing methods and analysis, and building humanized mice were equally ranked.

Figure 1. Stakeholder priorities for mouse model research coded to 36 keywords.



CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats

PDX = patient-derived xenografts

TME = tumor microenvironment

The priorities of each stakeholder group were analyzed separately and are described below, along with a qualitative assessment of distinguishing characteristics of each group.

### *Academic Basic Researchers*

The basic research stakeholders primarily held Assistant, Associate, or full Professor positions within their respective academic institutions. Several were Department Chairs or Deans. Many of the academic basic researchers wrote animal protocols, directed the experiments of the graduate student and postdoctoral fellow trainees, and analyzed data. Basic researchers identified the following as their top five priorities:

1. Improving communication and collaboration between researchers.
2. Supporting private-academic partnerships.
3. Increasing funding for mouse model research.
4. Increasing awareness of the importance of mouse model research.
5. Standardizing methods and analysis.

Basic researchers commented on the need for study section reform more frequently than other stakeholder groups. Along with their translational colleagues, they also tended to prioritize exploratory and descriptive research more so than other groups. During the interviews, basic researchers emphasized how *in vivo* findings from mice can be used to inform and direct the next laboratory bench experiments, and vice versa. Although many of the researchers perform cell culture experiments, they acknowledged the importance of studying responses in an organismal context. Basic researchers were more likely to mention the use of mice in monitoring the function of specific genes in cancer and to study basic developmental and disease processes. Many of these researchers also study basic developmental processes to identify how tumors might originate. Many basic academics professed the desire to create strains and tools that are useful for other scientists.

### *Academic Clinical Researchers*

Clinical researchers included stakeholders who possess an M.D. degree and participate in research related to clinical trials within an academic institution. Clinical researchers identified the following as their top five priorities:

1. Improving communication and collaboration between researchers.
2. Supporting private-academic partnerships.
3. Developing a mouse model database.
4. Characterizing and validating models.
5. Focusing on comparative biology.

Clinical researchers, along with their translational colleagues, cited the importance of using mice to improve imaging technology. Clinical, basic, and translational researchers all recognized the importance of including strong pathology expertise in each translational project. A higher proportion of clinicians, compared to other stakeholder groups, mentioned the need to study drug combinations. Academic clinical researchers were more likely than others to collaborate with laboratories that conduct mouse research to inform human clinical trial design and make decisions about which drugs should proceed to clinical trials. Clinical researchers mentioned the high regulatory burden of preclinical and clinical research. Some scientists, for example, must follow internal review board, animal, and therapeutics protocols—all of which must meet Federal regulations.

### *Academic Epidemiological Researchers*

Individuals in the epidemiologist category included academics who specialized in population-based research. This group was the hardest to locate and convince to interview, because many epidemiologists do not have direct experience with mouse models due to the nature of their research. Epidemiological researchers were identified from relevant NIH grant award lists and through NCI recommendations. Further efforts to identify experts focused on contacting individuals within Cancer Epidemiology or other related departments at R01 institutions. Epidemiological researchers identified the following as their top five priorities:

1. Improving communication and collaboration between researchers.
2. Supporting private-academic partnerships.
3. Focusing on genetics and genomics.
4. Focusing on environmental exposures and cancer risk.
5. Characterizing and validating models.

Compared to the other groups, epidemiologists focused more on the need to study environmental exposures (single and combined exposures) and cancer risk factors. They tended to be concerned with developing policies and preventive measures that could avert disease, rather than focusing on drug development. Epidemiologists were the least likely to mention funding limitations as a challenge to mouse model research (most likely because many do not work directly with mice) and least often cited the need for a model database.

Epidemiologists attempt to understand populations and determine risk factors for the development of cancer, progression, treatment outcomes, or survivorship. They noted that animal models can inform every step of the process, provided that the animal models appropriately recapitulate human exposure and molecular pathogenesis.

### *Academic Translational Researchers*

Academic translational researchers included individuals who work across a continuum of research, from basic through clinical applications. Translational researchers were more likely to perform mouse experiments and contribute to human trials. Translational researchers identified the following as their top five priorities:

1. Improving communication and collaboration between researchers.
2. Supporting private-academic partnerships.
3. Developing a mouse model database.
4. Characterizing and validating models.
5. Increasing funding for mouse model research.

Translational researchers cited the need for training and access to core facilities more often than those in other groups. They also focused on the benefits of integrating preclinical and clinical studies. Translational and clinical researchers alike emphasized the importance of comparative biology.

### *Private Sector Researchers*

The private sector scientists hailed from small biotechnology companies, large pharmaceutical institutions, and private or nonprofit research organizations. These scientists rely heavily on mouse models in preclinical work to define mechanisms of action and determine appropriate dosing strategies. Private sector researchers identified the following as their top five priorities:

1. Improving communication and collaboration between researchers.

2. Developing improved PDX models.
3. Supporting private-academic partnerships.
4. Increasing funding for mouse model research.
5. Characterizing and validating models.

More so than other groups, private sector researchers emphasized the need to build a community-wide repository for GEMM and PDX models. Private sector investigators noted that sharing of proprietary materials and data is not always possible because it can reduce a company's competitive advantage. Some stakeholders voiced reluctance to share data, while others encouraged the construction of mechanisms to facilitate data sharing across the field. Private sector researchers opined that industry requires higher standards to move drugs into the clinics, and several scientists called for better standardization and more rigor in animal studies.

## CONCLUSIONS

To determine priorities for the NCI's future efforts related to the use of mouse models in the cancer research community, 100 stakeholders were interviewed. The experts interviewed were representative of those in both academia and the private sector who use mouse models for transdisciplinary research; researchers developing mouse models; researchers using other techniques and/or model organisms (e.g., cell culture or rats) for basic research, which would have the capacity for translational research if a relevant mouse model was developed; clinicians who treat diseases for which no mouse models exist; epidemiologists who utilize data from mouse models to inform their research; and other researchers who have an interest in promoting translational science.

The most striking conclusion of the study was the uniformity of responses across all of the stakeholder groups. In fact, the two highest priorities overall (communication and private-academic partnerships) occupied the top three spots in all of the individual stakeholder groups, and many of the overall top ten priorities were also present in the top ten priorities of the individual stakeholder groups. From this analysis, the NCI's programmatic priorities are clear. The Institute should consider focusing on fostering communication and collaborations (including private-academic partnerships), improving awareness of mouse model research, supporting the characterization and validation of mouse models, developing a model database to house characterization data, and addressing the funding limitations of mouse research.

### *Potential Focus Group Topics*

Focus groups are planned as part of the NCI-MMHCC needs assessment. The vast majority of the stakeholders interviewed expressed a willingness to participate in the subsequent focus groups. The results of the interviews were intended to develop relevant focus group questions; an analysis of the interview results identified several high-priority issues that could be investigated in further detail during the focus groups. Potential focus group questions include:

1. How can the NCI most easily promote multidisciplinary collaboration?
2. How can the NCI spread awareness and educate the cancer research community about the benefits and uses of mouse models?
3. How can the NCI organize a task force to characterize the available models and determine the ways in which each recapitulates human disease?
4. What information should a mouse models database include?
5. How can experiments and data analysis be standardized?
6. What are the best outcomes to measure?
7. What specific funding mechanisms would be the most useful to develop?



Optimal focus group questions will be crafted in collaboration with the NCI to ensure that the goals of the needs assessment are met. The information collected during the interview and focus group phases of the needs assessment will be used by the NCI to determine the most effective ways to promote the use of mouse models for translational research.

## APPENDIX A. INTERVIEW GUIDE

OMB Number: 0925-0046  
Expiration Date: 05/31/2016

### Interviews with Stakeholders of National Cancer Institute's (NCI) Mouse Models Resources

#### **Burden Statement**

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0046). Do not return the completed form to this address.

#### **Introduction**

Thank you for consenting to participate in this interview to expose the opportunities and challenges for the use of mouse models in cancer research. As you are aware, the National Cancer Institute (NCI) is conducting this interview to obtain information on the degree of awareness of the mouse and human-in-mouse models that support basic, translational, clinical, and epidemiological research applications, how satisfied you are with these resources, and how we can improve and promote the program and communication among the various stakeholders in the cancer research community. Do you have any questions about the information that you have received regarding this stakeholder satisfaction interview?

#### **Overview of the Process**

This interview will last approximately 30 minutes. The information and opinions that you provide will be used to determine how the cancer research community develops and uses mice and mouse and human-in-mouse models, the evolution of standard practices in the development and use of mouse models, and future directions in these areas. The information that you provide will be kept secure to the extent provided by law; we will not attribute quotes or specific perspectives to you. Your responses will be audio-recorded to ensure that your comments are captured accurately. The audio files will be deleted at the end of the project.

#### **Interview Questions**

1. Please indicate your title and role in your organization. How long have you served in this role?
2. In what capacity do you use mouse models, human-in-mouse models, or data generated from them in your current work (and former work history)?
3. From your perspective as a [academic basic, translational, clinical, epidemiological, private sector] researcher, what research questions need to be addressed using translational mouse models (e.g., type of cancer, specific signaling pathways)?

4. Please describe any emerging opportunities for fully integrating mouse models or data from mouse models in [academic basic, translational, clinical, epidemiological, private sector] research applications (e.g., cutting-edge human-in-mouse experiments, computational methods).
5. What current challenges exist to fully integrating mouse models in [academic basic, translational, clinical, epidemiological, private sector] research applications, and how can these challenges be addressed (e.g., technology needs, supporting infrastructure, databases)?
6. What capacity, knowledge, and skills does the [academic basic, translational, clinical, epidemiological, private sector] research community need to develop to make the best use of mouse models as translational research tools (e.g., improved study design, training, statistical analyses)?
7. What collaborations can be developed to foster best practices for pre-, co-, and post-clinical applications of mouse models (e.g., public-private partnerships, opportunities to share data)?

### **Follow-Up**

Following the conclusion of the interviews, the NCI will conduct focus groups based on the analysis of interview responses to better understand the specific needs of academic basic, translational, clinical, epidemiological, and private sector researchers. Please let us know if you would be interested in participating in a focus group in the Fall of 2014<sup>4</sup>.

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<sup>4</sup> If focus groups are planned, a separate PRA/OMB clearance will be requested to conduct these.

## APPENDIX B. INVITATION

### Email Invitation for the Stakeholder Satisfaction with the National Cancer Institute's Mouse Models Services and Products

Subject Line [High Importance]: Request for Participation in an NCI Stakeholder Satisfaction Interview

Dear Dr. \_\_\_\_\_,

You have been identified as a key stakeholder who can provide important insights to inform how to improve and promote the use of mouse models and continue the evolution of standard practices for use of mouse models in the fields of basic, translational, clinical, and epidemiological research in academia, as well as private sector research. We would appreciate your participation in a National Cancer Institute (NCI) stakeholder satisfaction interview to better understand the challenges and opportunities for a widely deployed suite of cancer models to support basic research and translational applications within the cancer research community.

As you know, mouse and human-in-mouse models are employed in basic, translational, clinical, population, and pharmaceutical and biotechnology research. The quality of the research using mouse models depends on the reliability of the data that are generated from the animals, the appropriate selection of models used, and guidance on best practices that ensure robust experimentation in mouse models. As research using mouse models has expanded, concerns have been raised about the reliability and robustness of the models, and about how well the resulting experimental data inform research that is designed to benefit patients directly.

To address these issues, the NCI began 4 years ago to explore the variety of ways that mouse and human-in-mouse models are used in all facets of cancer research. For example, the NCI launched an international project on standard practices and operating procedures to help guide those in the cancer research community who are new to using mouse models or who are experienced modelers attempting to use their models for a different application. This project resulted in the publication of a methods book to guide translational applications (<http://cshprotocols.cshlp.org/content/2013/11/pdb.top078774.long>). The NCI now requires an assessment of the academic and private sector cancer research community to identify important research resource, training, and collaborative opportunities for mouse and human-in-mouse models of human cancer. This assessment will be accomplished through stakeholder interviews with experts such as yourself.

The NCI recently released several Funding Opportunity Announcements (FOAs) related to the application of mouse models for translational research:

Oncology Models Forum (U24):

<http://grants.nih.gov/grants/guide/pa-files/PAR-14-239.html>

Collaborative Research Projects to Enhance Applicability of Mouse Models for Translational Research (Collaborative R01):

<http://grants.nih.gov/grants/guide/pa-files/PAR-14-240.html>

Research Projects to Enhance Applicability of Mouse Models for Translational Research (R01):

<http://grants.nih.gov/grants/guide/pa-files/PAR-14-241.html>

Your input during this interview will be very important to the cancer research community, as your responses will be used to determine the most important research questions to address using translational mouse models; emerging opportunities or persistent challenges related to mouse model research; and collaborative opportunities designed to leverage other relevant efforts at governmental, academic, nonprofit, or private sector institutions.

If you agree to participate and contribute your important insights, I will contact you on behalf of the NCI to schedule a time for a 30-minute telephone interview. If you do not believe that you can participate in this essential interview, please let me know, and please consider providing the name of an appropriate individual within your organization who might be willing to contribute. For additional information about the NCI's mouse models resources, please visit <http://emice.nci.nih.gov>. If you have any questions, please contact me using the information below, or contact study director Dr. Jennifer McCulley at The Scientific Consulting Group, Inc. by telephone or email (301-670-4990, [jmcculley@scgcorp.com](mailto:jmcculley@scgcorp.com)).

Thank you in advance for your time and thoughtfulness.

Sincerely,

[Name of Interviewer]

On Behalf of the NCI  
[Signature Lines]

## APPENDIX C. CONSENT FORM

### Informed Consent for the Stakeholder Satisfaction with the National Cancer Institute's Mouse Models Services and Resources

OMB Number: 0925-0046  
Expiration Date: 05/31/2016

Public reporting burden for this collection of information is estimated to average 5 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0648). Do not return the completed form to this address.

#### Purpose and Benefits

Mouse and human-in-mouse models are employed in the continuum of cancer research activities. The quality of that research depends on the reliability of the data that are generated, appropriate selection of models, and standard practices that ensure robust experimentation. Recently there have been concerns about the reliability and robustness of mouse models and how well the resulting data inform clinical practice. The National Cancer Institute (NCI) launched a project on standard practices and operating procedures to guide cancer researchers who are new to using mouse models and experienced modelers using their models for different applications. The resulting methods book (<http://cshprotocols.cshlp.org/content/2013/11/pdb.top078774.long>) guides translational applications. The NCI requires an assessment of the academic and private sector cancer research community to identify important research resource, training, and collaboration opportunities for mouse and human-in-mouse models of human cancer.

You have been identified as a key stakeholder who can provide important insights to inform how to improve and promote the use of mouse models and continue the evolution of standard practices for mouse model use in the fields of basic, translational, clinical, and epidemiological research in academia and the private sector. We appreciate your voluntary participation in this stakeholder satisfaction interview.

#### Procedures

The Scientific Consulting Group, Inc. (SCG) and American Institutes for Research (AIR) are conducting the interviews on behalf of the NCI. SCG will select interviewees from five stakeholder groups: Academic basic, translational, clinical, and epidemiological researchers, and private sector researchers. SCG and AIR will conduct Interviews with selected stakeholders via telephone. If you consent to participate, we will contact you by email to schedule a 30-minute telephone interview. Research questions will relate to your current use of mouse and human-in-mouse models and your insights into the cancer research community's needs. SCG will record your responses to ensure accuracy. The audio files will be deleted following the interview. The information that you provide will be kept secure to the extent provided by law. Only the NCI and contractor project staff will have access to the interview responses. The information we collect from you will be combined with information from other research participants to help develop a profile of community needs. We will not attribute any information obtained to a specific individual.

**Risks and Benefits**

The overall benefits of the stakeholder satisfaction assessment for the cancer research community will be significant. We expect that it will improve the translation of research involving mouse models to clinical applications that reduce the burden of cancer in humans. You can refuse to answer any question, and you can stop your participation in the interview at any time if you feel uncomfortable. If you have any questions about this interview, including potential risks and benefits, please contact the project coordinator at SCG, Dr. Jennifer McCulley (jmcculley@scgcorp.com or 301-670-4990).

**Informed Consent**

The interviews regarding the mouse models services and resources of the National Cancer Institute (NCI) have been explained to me. I voluntarily consent to participate. I have had an opportunity to have my questions answered. I know that I may refuse to participate or to stop my participation in the interview at any time. I understand that if I have questions about this project or my rights as a respondent, I may contact the project coordinator.

\_\_\_\_\_

Participant Signature

\_\_\_\_\_

Date

\_\_\_\_\_

Interviewer Signature

\_\_\_\_\_

Date

## APPENDIX D. INTERVIEW KEYWORDS

### Research Questions and Emerging Opportunities

Biomarkers  
Cancer Prevention  
Drug Combinations  
Exploratory Research  
Exposure/Risk  
Genetics/Genomics

Heterogeneity  
Initiation  
Metastasis  
Resistance  
Tumor Microenvironment (TME)

### Mouse Model Improvement

Accuracy/Representation  
Comparative Biology  
Humanized Mice

Other Models  
Patient-Derived Xenograft (PDX) Models  
Validation/Characterization

### Cancer Research Community Resources

Awareness  
Communication/Collaboration  
Core Facilities  
Database (Data)  
Funding  
Meetings/Workshops

Pathology  
Quality Control  
Repository (Models)  
Standardization  
Study Sections  
Training

### Development of Tools and Techniques

Bioinformatics  
Clustered Regularly Interspaced Short  
Palindromic Repeats (CRISPR)

Imaging  
Statistics  
Study Design

### Collaborations

Multidisciplinary Teams  
Private-Academic Partnerships



## APPENDIX E. STAKEHOLDER CHARACTERISTICS

### Stakeholder Affiliations

AstraZeneca	Stanford University
Baylor College of Medicine	Teva Pharmaceuticals Industries, Ltd.
Beth Israel Deaconess Medical Center	The Johns Hopkins University
BioMarin	The Ohio State University
Biomodels	The University of Alabama, Birmingham
BluePrint	The University of Hawaii
Bristol-Myers Squibb Company	The University of Texas, MD Anderson Cancer Center
Cincinnati Children's Hospital	The University of Texas Southwestern Medical Center
Cold Spring Harbor Laboratory	University of Washington, Fred Hutchinson Cancer Center
Cornell University	University of California, Davis
Dartmouth College	University of California, Irvine
Duke University	University of California, San Diego
Five Prime Therapeutics	University of California, San Francisco
Genentech	University of Cincinnati
Georgetown University	University of Illinois
Harvard Medical School	University of Louisville
Indiana University School of Medicine	University of Massachusetts
Jackson Laboratories	University of Michigan
Kings College	University of Minnesota
Massachusetts Institute of Technology	University of Pennsylvania
Mayo Clinic College of Medicine	University of Southern California
MedImmune	University of Tennessee Health Science Center
Memorial Sloan-Kettering Cancer Center	University of Toronto
Merck	University of Utah
Moffitt Cancer Center	University of Virginia
Novartis	Vanderbilt University
Oklahoma Medical Research Foundation	Washington University
Pacific Northwest Diabetes Research Institute	Yale University
Plexxicon	
Sanford-Burnham Medical Research Institute	
Sanofi-Aventis	

### Stakeholder Titles

Assistant Professor	Deputy Director
Associate Director	Director
Associate Member	Executive Director
Associate Professor	Faculty Member, Associate Head of Research
Associate Professor and Director	Principal Investigator
Attending Physician	Principal Scientist
Chairperson and Professor	Professor
Chief	Professor and Associate Director
Chief Executive Officer	Professor and Chair
Consultant	Professor and Director
Dean	Professor and Vice Chair
Department Chair	Professor and Vice Dean

Professor, Associate Director, and  
Division Chief  
Professor, Associate Dean, and Co-Director  
Professor Emeritus and Senior Scientist  
Professor in the Department of Medicine  
Program Director  
Research Assistant Professor

Scientist 2  
Senior Director  
Senior Member  
Senior Scientist  
Senior Vice President and Director  
Team Leader  
Vice President

### Stakeholder Research Topics

Acute Lymphoblastic Leukemia  
Autoimmunity  
Brain Cancer  
Breast Cancer  
Cancer Biology  
Cancer Stem Cells  
Cell and Developmental Biology and  
Pancreatic Cancer  
Colon Cancer  
Colorectal Cancer  
Developmental Biology  
Diagnostic Pathology in Humans and  
Biomedical Informatics  
Gastric and Colon  
Glioblastoma  
Immuno-oncology  
Intestinal Cancers  
Leukemia

Liver Cancer  
Lung Cancer  
Medulloblastoma  
Melanoma  
Muscle and Bone Tumors  
Oral Cancer  
Ovarian Cancer  
Pancreatic Cancer  
Peripheral Nerve Tumors  
Pharmacology  
Preclinical Oncology  
Prostate Cancer  
Sarcomas  
Skin Cancer  
Squamous Cell Carcinoma  
Testicular Cancer  
Tumor Microenvironment