Article

Mouse model: what do Japanese life sciences researchers mean by this term?

Jin Higashijima, Kae Takahashi, Kazuto Kato

ABSTRACT: *Mouse-related research in the life sciences has expanded remarkably over the last two decades, resulting in growing use of the term "mouse model". Our interviews with 64 leading Japanese life sciences researchers showed heterogeneities in the definition of "mouse model" in the Japanese life sciences community. Here, we discuss the implications for the relationship between the life sciences community and society in Japan that may result from this ambiguity in the terminology. It is suggested that, in Japanese life sciences, efforts by individual researchers to make their scientific information unambiguous and explanative are necessary.*

Context

The laboratory mouse is one of the most commonly used experimental animals in life sciences research.[1,2,3] Its numerous advantages, including established genetic techniques, abundant information from genomic decoding, genetic homogeneity, relatively short lifecycle and strong genomic homology with humans, have led to an explosion of research employing mice and mouse-related data in both biological and medical sciences.[4,5,6,7,8] Meanwhile, the term "mouse model" features prominently in scientific articles, press releases, documents and the texts of academic, scientific and research websites. A search on the term "mouse model" conducted in the ISI Web of Knowledge[SM], one of the largest online academic databases, reveals that between 5000 and 7000 published documents have used the term every year for the past five years.

Objective

But what really is a "mouse model" in the Japanese life sciences community? Do Japanese life sciences researchers give the term the same meaning when referring to mouse models of, for example, embryonic development versus autistic spectrum disorders?[9,10,11,12,13] Or, does the term mean different things to different researchers?[14,15] We conducted interviews with 64 life sciences researchers involved in mouse-related research in Japan. Here, we examine some heterogeneities found in the opinions of these life sciences researchers regarding the term "mouse model", and discuss some possible issues emerging from these heterogeneities.

Methods

Subjects

Sixty-four Japanese life sciences researchers (59 males, 5 females) were interviewed. All 64 respondents were conducting basic research involving mice. Except for a researcher whose mother language was English (but could speak Japanese very well and was interviewed in Japanese), the mother tongue of these researchers was Japanese.

   Respondent characteristics: (1) Academic degrees: Of the 64 participants, 26 held doctorates in *Medical Science* and 22 of these were medical doctors. Another 21 had doctorates in *Science*, of whom 1 was a

medical doctor. Among the remaining researchers, 8 had degrees in *Pharmaceutical Science*, 4 in *Agriculture*, 3 in *Psychology* and 2 in *Dental Science*. (2) Academic societies: The respondents were members of academic societies as follows: 73% belonged to The Molecular Biology Society of Japan; 39% to The Japanese Biochemical Society; 30% to The Japan Neuroscience Society; 25% to The Japanese Cancer Association; 25% to The Japanese Society of Developmental Biologists; 19% to The Japanese Society for Immunology; 14% to The Japan Society for Cell Biology; and 13% to The Pharmaceutical Society of Japan.

  Subject selection: The candidates were selected based on their numbers of published research papers, areas of research and academic positions. All participants had published more than 3 peer-reviewed academic papers and held academic positions (primarily associated and full professor status). We invited a total of 91 researchers to participate in the study by e-mail, of whom 68 responded favorably. From these 68 researchers, we selected 63 for formal participation. We also included 2 researchers who were recommended by participants without considering their academic positions.

Procedure

Interview: We used a semi-structured interview format, which is usually used to clarify the contents of specific problems.[16] Each interview lasted an average of 90 minutes, and consisted of a set of core questions presented in various orders across the respondents. To obtain the subject's opinions more accurately, the interview language was tailored to each subject's vocabulary and area of expertise. The core questions focused on: (1) the definition of each scientist's use of the term "mouse model"; and (2) the relationship between mouse-related research and human-oriented research. Other questions addressed (A) the ethical and social issues emerging from behavioral genetics and (B) the transmission of information from life sciences researchers to society, but these results are not discussed in this paper. The interviewer took notes during the interviews. To help the interviewer, an IC recorder was also used in roughly one-third of the interviews with the subjects' permission. After each session, the interviewer prepared a written record of the interview based on all records.

  Analysis: For data analysis, each data set was first classified to obtain a category list. Based on this list, the data were further classified by 2 coders, each of whom scored 0.5 points if the answer corresponded with a relevant item on the category list. The sum of points assigned to each item on the list was divided by the number of respondents (modified percentage of respondents). Thus, if the modified percentage of respondents for item 'A' on the list was 45, approximately 45% of the respondents answered 'A'. The total modified percentage of respondents was not always 100 because some respondents did not answer all the questions owing to interview time limitations. To assess inter-coder reliability, we calculated the percent agreement. If the percent agreement was 95%, the classifiers' agreement with respect to scoring of the answer was 95%. The number of coinciding agreements due to chance was presumed to be low because of the diversity of the responses. Finally, the overall percentage of agreement was above 95%.

Results

What is the definition of a "mouse model"? The term was used by nearly 80% of the respondents (Figure 1). Our analysis revealed at least 4 dimensions of its use, namely *biological similarity*, *experimental methods*, *purpose of research* and *academic consensus*, which were further subdivided according to the descriptions contained in Figure 2. In this analysis, we mainly intended to show that each researcher's use of the term "mouse model" has various aspects. In other words, we did not aim to claim that each researcher's use of the term should be restricted in only one of these 4 dimensions. For that reason, it should be noted that these 4 dimensions are not necessarily mutually exclusive.

  About half the respondents (51%) raised the phenotypic resemblance to humans in the *biological similarity* dimension (Figure 2, B) and/or future directions of each research project for application to human diseases (49%) in the *purpose of research* dimension (Figure 2, D) as the main definition. In addition, 22% of the respondents mentioned that it was necessary to have a common gene responsible for a given disease between humans and mice (Figure 2, B). As a whole, the respondents did not appear to have consistent and common definitions either within or among the 4 dimensions. For example, some respondents emphasized the existence of common genes between humans and mice, while others saw the
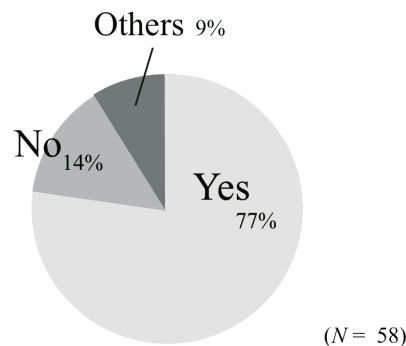
Figure 1. Answers to the question "Do you use the term mouse-model?"
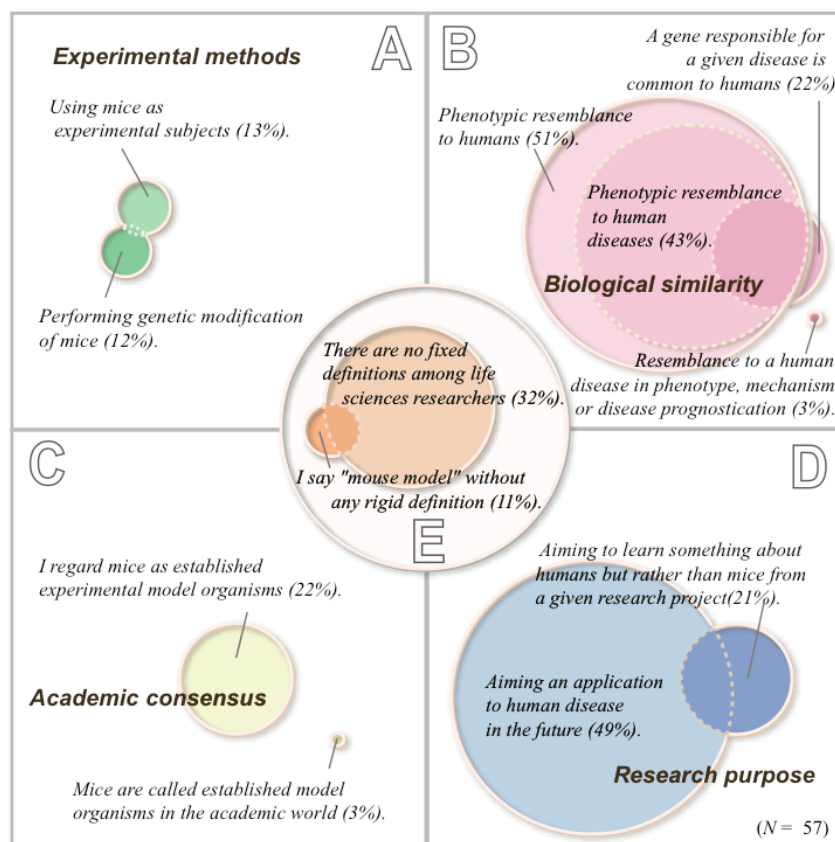

Figure 2. Definitions of the term"mouse model" (Multiple answers allowed). Note that these demensions are not mutually exclusive.

phenotypic resemblance between humans and mice as the main requirement to refer to a given mouse research project as a mouse model (Figure 2, B).

The main reasons why Japanese life sciences researchers used the term also appeared to differ (Table 1). In general, the Japanese life sciences researchers had individual intentions or criteria of which dimensions to highlight by way of using the term. The majority (43%) used it to appeal to some *relationship* between their mouse research and humans'. Meanwhile, a non-negligible number of respondents (17%) reported using the term to emphasize the *subject* of the research, i.e., they used the term "mouse model" to show that their research was carried out with mice. Many of them used the term "mouse model" to indicate that their research results were only applicable to mice. Regarding this point, Table 2 shows some detailed comments emphasized by the respondents for existing mouse-related

To indicate that a given mouse-related research project has some relationship to humans (43%).

    To show a resemblance between their mouse research and humans' (18%).
      ------- *Especially between a mouse disease and a human disease (13%).*
    To show that a research project is human-oriented (9%).

The term is easily applicable in various explanations (25%).

To emphasize that a research project involves a mice not humans (17%).

To indicate the usefulness of a research project (9%).

There is an academic consensus to use the term "mouse model" (3%).

Others (10%).

(*N* = 58)

Table 1. Reasons why Japanese life sciences researchers use the term "mouse-model" (*Multiple answers allowed*).

Methods of quantification and/or measurement are indispensable, when using mouse models as research tools for learning something about humans (33%).

Mouse models alone are insufficient for learning something about humans (25%).

Mice and humans are obviously different creatures, although mice are used in many human-oriented life sciences research (17%).

I have doubts about some existing mouse models (10%).

The reliability, effectiveness and limitations of each mouse model is need to be shown (7%).

(*N* = 53)

Table 2. Comments on existing mouse-related studies and mouse models (Multiple answers allowed). Note that these comments are not mutually exclusive.

studies and mouse models. Some respondents considered it important for all life sciences researchers addressing items using the term "mouse model" to sufficiently explain or clarify the differences and distances between humans and mice (7%).

Regarding the current trend in the usage of the term "mouse model" in the Japanese life sciences community, some respondents made critical comments (Table 3). These comments were made by highly recognized researchers with established careers as life sciences researchers as well as reviewers or evaluators of academic papers and/or research projects (in the academic community, it is the reviewers of individual academic journals who make the decision regarding whether each mouse-related research project is valid and can or cannot be referred to as a "mouse model"). For example, 20% of the subjects pointed out that the term tended to create too many social expectations and 9% felt that life sciences researchers should use the term with more limitations. A further 3% expressed a belief that Japanese life sciences researchers tended to use the term too easily. In a somewhat different vein, 7% of respondents argued that, in Japanese grant applications, some researchers use the term "mouse model" to suggest that their mouse-related research projects had a strong possibility of direct applications in humans, regardless

The term "mouse model" tends to create too many social expectations (20%).

Japanese life sciences researchers should use the term "mouse model" with more limitations (9%).

Some Japanese life sciences researchers only use the term "mouse model" because they want to show the proximity between their research projects and applications to humans, regardless of the actual proximity (7%).

Japanese life sciences researchers tend to use the term "mouse model" too easily (3%).

(*N* = 58)

Table 3. Critical comments on the trend of the usage of the term "mouse model" in the Japanese life sciences community (*Multiple answers allowed*).

of whether or not they actually did. In other words, there was a concern that some life sciences researchers only use the term "mouse model" because they want to show the proximity between their research projects and applications to humans, regardless of the actual proximity. Our respondents said that these kinds of researchers use the term "mouse model" without any valid criteria, other than the fact that they use mice in their research projects. Our respondents showed critical attitudes toward the present Japanese research grant system, which overemphasizes the applicability of basic research to humans. With regard to this point, 30% of our respondents suggested that they used the term predominantly and/or only in research grant applications.

Discussion:

In summary, the term "mouse model" appears to be used in several contexts by Japanese life sciences researchers to highlight different aspects of a given area of research. Our results have clarified the two opposite meanings contained in the term "mouse model". That is, the term is occasionally used to stress the "basic" nature of certain research and in other cases to emphasize an aspect of "applied" research in Japan. Since it is not always easy to tell which aspect is intended, it is possible that these opposite meanings may be confusing in communications between the life sciences community and society in Japan, or, taking the long-term view, among the Japanese life sciences community in some cases.

1. *Communication between life sciences researchers and society in Japan:* In light of our findings, we suggest that distributing scientific information using the term "mouse model" either directly to the public or via the mass media may cause confusion or, in some cases, social misunderstandings as a result of ambiguities inherent in the use of this term with multiple meanings, especially regarding the applicability to humans of each mouse-related research project. In Japan, we can see the terms "mouse model" and "model mouse" in press releases on the web published by some universities and research institutes with top-class public relations sections, such as RIKEN, The University of Tokyo and Kyoto University. Although scientific information is highly specialized and much of it is restricted to the scientific community, in the case of the term "mouse model", it is no longer restricted to the scientific community in some minds.

   We should also consider the fact that the general public tend to attach different meanings to scientific terms, which researchers belonging to the scientific community do not intend to mean. For example, it was reported that the word "mutation" has acquired a negative meaning in American society, suggesting that every mutation must cause a genetic disease.[17] Unlike other terms with multiple meanings, such as gene,[18,19,20], which have already established cultural citizenship in society, the scientific term "mouse model" needs to be used more carefully by life

sciences researchers in Japan. Without sufficient scientific knowledge to provide context, it is difficult to know whether the term "mouse model" is intended to emphasize the "human-oriented" aspect of a given research project or is just describing a "phenotypic resemblance" (*between-dimension differences* in Figure 2), not to mention the difference between "similarity in a causative gene" and a "phenotypic resemblance" (*within-dimension differences* in Figure 2).

Although it is often the case that scientific terms may be interpreted in several ways by various people, Japanese life sciences researchers should remain cautious of the differences.[21] From our results, it is undeniable that, in some cases, using the term "mouse model" consequently implies that a given mouse-related research project is possibly applicable to humans, regardless of whether or not this is intended. In fact, some researchers in our study reported personal experiences that, after publication of their research, incorrect (from the researchers' point of view) mass-media coverage stressing the "application to humans" aspects of their research projects had occurred. After publication, whether via the mass media or direct receipt, it is up to each member of society to interpret and examine the given scientific information.[22] Our results imply that case-by-case differences in the relationship between a given mouse-related research project and humans are far more difficult to understand, even for life sciences researchers in some cases.[23] Thus, if Japanese life sciences researchers are motivated to establish effective communication with the wide range of members of Japanese society, with regard to the "applicability to humans" of mouse-related studies, it may be a good idea to refine their usage of the term "mouse model", either by adding more explanative information or finding alternative, more carefully defined, terms to make their information more explanative and understandable for society. Insensible usage of the term "mouse model" may damage the confidence of Japanese society in Japanese life sciences researchers.

2. *Communication among Japanese life sciences researchers:* With the recent disciplinary segmentation produced by the highly specialized nature of the life sciences, our results suggest that in Japan, even for life sciences researchers, it may be difficult to infer the correct meanings for each mouse-related research project described by the vague opposite meanings of the term "mouse model". The growing number of scientific papers reviewing "mouse models" may reflect the difficulties[13, 14] faced by individual life sciences researchers today to cover all related fields with the recent diversity of mouse-related research. For example, overall, 42% of our respondents reported that it was difficult to evaluate the relevance and applicability of mouse-related research projects to the human brain or mental activities,[23] which are highly transdisciplinary fields. Moreover, within specific academic disciplines, there exist more complex qualitative differences. For example, in the case of bipolar disorder, there are 3 kinds of mouse models, namely symptom-based models, endophenotype- and pathophysiology-based models and models based on responses to existing medications.[14,24] Seemingly, our results suggest that, other than the fact that a given research project is related to mice, there are no consistent meanings for the term "mouse model". Life sciences research is comprised of interdisciplinary fields and it is the interdisciplinarity of these fields that makes great contributions to human knowledge. It is dismissive that a terminology problem, such as usage of the term "mouse model", may inhibit interdisciplinary efforts in the Japanese life sciences community.

    We speculate that at least 3 contributory factors interact to produce the ambiguities we have discussed. First, as we have mentioned several times, it should be noted that the life sciences are comprised of transdisciplinary fields. The integral approach necessitated by multidisciplinary research is one possible explanation for the variations in the meaning of the term "mouse model" shown in our results. Second, as Condit and Railsback suggested in their 2007 case study of zinc finger proteins, it appears that recent changes in the approach to the classification and generalization processes of scientific findings in the life sciences, namely a shift from "identity-based" to "similarity-based" generalization, play important roles in complicating common terminologies.[25] A lack of awareness of these changes among Japanese life sciences researchers may serve to increase the occurrence of ambiguous usages. Finally, in Japan, implicit or explicit social pressure on the life sciences to increase the visibility of possible research applications, as suggested in our results, may encourage some researchers to use the term "mouse model" with less precision.

Limitations

We should point out that our study merely demonstrates the existence of heterogeneous opinions among life sciences researchers in Japan, owing to our semi-qualitative experimental method. Although the interviews included researchers in fields as diverse as bioinformatics, molecular mechanisms, protein functions, neural cells and behavioral analysis, we do not aspire to a representative sample of life sciences as a whole.

Conclusions

The life sciences have enormous influence on society and account for a large percentage of public research funding in Japan. It is therefore important that the quality of information transmission from life sciences researchers to society in Japan is as high as possible.[26,27] In this article, we have discussed some possible implications emerging from ambiguous and contradictory meanings of the term "mouse model". It is suggested that Japanese researchers make an effort to refine their use of this term. We must stress again the amazing degree of specialization that characterizes scientific knowledge in contemporary Japan, and difficulties in comprehending scientific information on the part of the general public are of great importance and concern. In the context of the rapid progress in life sciences fields, efforts by individual researchers to make their scientific information unambiguous and explanative may be necessary to build a good relationship between Japanese life sciences researchers and society, and, in some minds, for the advancement of Japanese life sciences. This approach is likely to be far more effective than simply relying on development of the scientific literacy of the mass media and the general public, at least in the short term. An examination of the variety in the "meanings" of each technical term is important when communicating information based on individual research projects to Japanese society. We hope that our results will provide Japanese life sciences researchers and others with a broader understanding of mouse-related research, with regard to Japanese life sciences researchers' terminology and interpretation of whole research fields.

Acknowledgments:

Notes and references

[1] J.T. Eppig, J.A. Blake and C. J. Bult (2008), *The mouse genome database (MGD): mouse biology and model systems*, *Nucleic Acids Res* **36**, D724.

[2] R. Mott (2007), *A haplotype map for the laboratory mouse*, *Nat Genet* **39**(9), 1054.

[3] D.R. Beier (2005), *Animal models*, Encyclopedia of life sciences, John Wiley & Sons, available at:
<http://mrw.interscience.wiley.com/emrw/9780470015902/els/article/a0005680/current/html>

[4] M.S. Boguski (2002), *Comparative genomics: the mouse that roared*, *Nature* **420**(6915), 515-516.

[5] A. Bradley (2002), *Mining the mouse genome*, *Nature* **420**(6915), 512-514.

[6] Mouse Genome Consortium (2002), *Initial sequencing and comparative analysis of the mouse genome*, *Nature* **420**(6915), 520-562.

[7] C.M. Egan et al. (2007), *Recurrent DNA copy number variation in the laboratory mouse*, *Nat Genet* **39**, 1384-1389.

[8] D. Wahlsten et al. (2003), *In search of a better mouse test*, *Trends Neurosci* **26**(3), 132-136.

[9] J.E. Talmadge et al. (2007), *Murine models to evaluate novel and conventional therapeutic strategies for cancer*, *Am J Pathol* **170**(3), 793-804.

[10] V. Lammemand-Breitenbach et al. (2005), *How patients have benefited from mouse models of acute promyelocytic leukaemia*, *Nat Rev Cancer* **5**(10), 821-835.

[11] R.A. Jenner and M.A. Willis (2007), *The choice of model organisms in evo-devo*, *Nat Rev Genet* **8**(4), 311-319.

[12] L.H. Tecott (2003), *The genes and brains of mice and men*, *Am J Psychiatry* **160**(4), 646-656.

[13] S.S. Moy and J.J. Nadler (2008), *Advances in behavioral genetics: mouse models of autism*, *Mol Psychiatry* **13**(1), 4-26.

[14] T. Kato, M. Kubota and T. Kasahara (2007), *Animal models of bipolar disorder*, Neurosci Biobehav Rev **31**(6), 832-842.

[15] T.C. Scharschmidt and J.A. Segre (2008), *Modeling atopic dermatitis with increasingly complex mouse models*, J Invest Dermatol **128**(5), 1061-1064.

[16] A.L. Kalfoglou et al. (2005), *Opinions about new reproductive genetic technologies: Hopes and fears for our genetic future*, Fertil Steril **83**(6), 1612-1621.

[17] C.M. Condit et al. (2004), *Lay people's understanding of and preference against the word "mutation"*, Am J Med Genet A **130**(3), 245-250.

[18] P.E. Griffiths and K. Stotz (2006), *Genes in the postgenomic era*, Theor Med Bioeth **27**(6), p. 499-521.

[19] M. Hayashi (2007), *Contexts of the Scientific Term: 'Gene' in Mass Media and Daily Use*, Proceedings of KEER 2007 International Conference of Kansei Engineering & Emotion Research, October 2007.

[20] L. Moss (2008), *The meaning of the gene and the future of the phenotype*, Genomics Soc Policy **4**(1), 38-57.

[21] V. Deretic and D.J. Klionsky (2008), *How cells clean house*, Scientific American Magazine, May, p. 74-81.

[22] D.R. Hayes (1992), *The growing inaccessibility of science*, Nature **356**(6372), 739-740.

[23] J. Higashijima, K. Takahashi and K. Kato (2008), *Heterogeneity among life sciences researchers: why should we seriously consider it?*, Proceedings of the Third International Applied Ethics Conference in Sapporo, November 2008.

[24] T.D. Gould and A. Einat (2007), *Animal models of bipolar disorder and mood stabilizer efficacy: A critical need for improvement*, Neurosci Biobehav Rev **31**(6), 825-831.

[25] C. Condit and L. Railsback (2008), *Generalization through similarity: motif discourse in the discovery and elaboration of zinc finger proteins*, BioMed Central **2**(3), 5.

[26] A.I. Leshner (2003), *Public engagement with science*, Science **299**(5609), 977.

[27] G. Pinholster and C. O'Malley (2006), *EurekAlert! survey confirms challenges for science communicators in the post-print era*, JCOM **05**(03), C01.

Authors

Jin Higashijima M.A., M.S. is a graduate student of the Graduate School of Biostudies, Kyoto University, Japan. She has studied the relationship between science and society, particularly focusing on behavioral genetics. E-mail: jin@lif.kyoto-u.ac.jp.

Kae Takahashi, M.S. was a graduate student of the Graduate School of Biostudies, Kyoto University, Japan. E-mail: Kaet@jamstec.go.jp.

Kazuto Kato Ph.D. (Science) is an Associate Professor of Science Communication and Bioethics at the Institute for Research in Humanities and Graduate School of Biostudies, Kyoto University, Japan. He is also an adjunct Associate Professor for Science Communication of the Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University. E-mail: kato@zinbun.kyoto-u.ac.jp.