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ILAR Reports

Standardized Nomenclature for Transgenic Animals

Committee on Transgenic Nomenclature

Institute of Laboratory Animal Resources

Commission on Life Sciences

National Research Council

Preface

As part of its mission to promote efficient, cost-effective, ethical research with animals, and to those ends to identify valuable laboratory animal resources, the Institute of Laboratory Animal Resources (ILAR) of the National Research Council's Commission on Life Sciences was charged with addressing a new and rapidly developing application of molecular biology to animal experimentation termed *transgenic technology*. The development of a large number of new strains of animals with this technology has been accompanied by some specific deficiencies, as follows:

- There is no standardized nomenclature by which to identify transgenic animals.
- There are no guidelines for managing animals that might be difficult to maintain and breed, have the potential for transmitting diseases to humans, or might have an adverse impact on the environment if inadvertently released.
- There are no effective mechanisms for ensuring the preservation of valuable transgenic models.

To address those deficiencies, the ILAR Council organized an advisory panel,^a which recommended a series of initiatives to assist scientists who work with or care for transgenic animals.

In recognition that the lack of a widely accepted standardized nomenclature for transgenic animals greatly complicates efforts to catalog existing resources, the recommended first initiative was that ILAR develop such a nomenclature. Accordingly, ILAR established the Committee on Transgenic Nomenclature to undertake this task and to delineate a means by which the nomenclature could be used to create a catalog of existing transgenic resources. The committee was constituted to include experts in the production of transgenic animals by various means, scientists with experience in issues related to animal nomenclature, and a member and an invited participant who are involved in the development of a data base on transgenic animals.

The committee felt that it would be sensible to establish a nomenclature that is compatible with the storage and efficient retrieval of information from the data base on transgenic animals. The nomenclature that it developed, therefore, includes the relevant differences in the various approaches to making transgenic animals, encompasses the diversity and complexity of the DNA elements that are introduced into the germline, and provides the conciseness required for the convenient use and efficient storage of information.

The committee acknowledges the assistance of the staff of ILAR, which has made this report possible.

Jon W. Gordon, *Chairman*

Committee on Transgenic Nomenclature

Footnote

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INTRODUCTION

The ability to achieve controlled genetic modifications of multicellular eukaryotic species by the insertion of genetic material, termed *transgenic technology*, has led to an explosion of research in developmental genetics, attracting the interest of many investigators who previously were not engaged in animal research. However, although many new animal models have been produced, there has been no organized effort to identify and catalog them. The lack of a catalog might keep research with the new technology from being conducted with maximal efficiency and effectiveness for several reasons:

- *Duplication of effort.* Many different transgenic animals already exist (perhaps as many as 10,000 strains). Without a catalog, investigators might needlessly reproduce existing models.
- *Loss of valuable transgenic models.* Many transgenic models are not relevant to the research programs of the laboratories in which they are made. When such models are made by insertional mutagenesis, they are often unique and irreplaceable. However, with today's funding constraints, laboratories cannot afford to maintain models that they are not using. In the absence of an effective method to make their existence known, such models would probably be discarded, even though they might be extremely valuable to investigators in other laboratories.
- *Loss of information.* Many of the subtleties of gene regulation are discernible only by comparing the expression of closely related transgenes in different strains. For example, only when different constructs of the human β -globin gene in transgenic mice were compared did it become apparent that DNA sequences derived from cloning vectors, such as bacteriophage or plasmids, could interfere with gene expression and that such interference could be overcome if multiple enhancer elements in the globin gene region were included in the transferred DNA construct. In the absence of a catalog of transgenic animals for comparative study, similar complexities of gene regulation might escape notice.

It is obvious that some registry of transgenic strains and their characteristics is essential. To that end, the Oak Ridge National Laboratory, Oak Ridge, Tennessee, under contract Y01 -ES10067 from the National Institute of Environmental Health Sciences of the National Institutes of Health has undertaken the development of a data base for cataloging transgenic animals: the Transgenic Animal Data Base (TADB). For the TADB to be effective and to promote effective communication between scientists in different laboratories, a widely accepted standardized nomenclature for transgenic animals is necessary.

ISSUES IN DEVELOPING A TRANSGENIC NOMENCLATURE

For developing a transgenic nomenclature, the committee defined a transgenic organism as an organism in which new genetic material has been experimentally introduced into the germ cells. The new DNA can be derived from the homologous species and need not be genetically active; however, it should be heritable. Thus, animals with new gene insertions resulting from ecotropic retroviral infection are not transgenic, nor are those receiving DNA only in somatic cells. In contrast, mice with an additional mouse β -globin gene that has been inserted into a site other than that of the endogenous gene and transmitted to progeny as a Mendelian trait are transgenic. Animals with genetic modifications introduced by homologous recombination in embryonic stem cells are considered transgenic if the purpose of the homologous recombination approach is to target functional genetic elements into specific sites in the genome.

A transgenic nomenclature must incorporate information related to both the methods used to produce transgenic animals and the diversity of genetic elements that can be inserted into animals. It must also be concise enough to make it easily recognized and remembered. Thus, there is a potential conflict between the need for conciseness and the need for completeness of information. The same conflict was encountered by the International Committee on Standardized Genetic Nomenclature for Mice, which began work on nomenclature for transgenes in 1984.

That committee proposed a general form that followed the format used for chromosomal anomalies: an abbreviation of the word *transgenic*, followed by parenthetical information on the inserted segment, followed by a unique laboratory code and a numerical designation. Although this nomenclature was widely circulated for review and the comments of experts in transgenic mice were incorporated, neither it nor the revised nomenclature published a few years later (Lyon, 1989a) has been widely used. A major problem has been deciding how much information on the inserted segment to include. Opinions vary from a three-character symbol to all the information known (the latter would sometimes mean a symbol that requires several lines of text).

Given that history and the present committee's own perception of the problems presented in creating a usable transgenic nomenclature, the committee decided that brief, unique identifiers of transgenic insertions would be most effective for transgene symbols. The full history and description of each transgenic insertion should be recorded in the TADB (described in detail in Appendix II).

In determining the elements of the transgene symbol, the committee concentrated its deliberations on the following issues:

- *The need to incorporate within the nomenclature a symbol that identifies important characteristics of the method used to create the new transgenic strain.* The committee concluded that it is important to distinguish between three approaches to making transgenic animals: methods that use modified retroviral vectors; gene-transfer methods, other than viral infection, that result in nontargeted (nonspecific) gene insertion; and targeted insertions (homologous recombination).
- *The need to identify the salient characteristics of the new genetic material and the consequences of its insertion into the genome.* The committee recognized that it would not be possible to incorporate within a short symbol all the important features of a given genetic modification. Genes from different species, orders, or even kingdoms can be readily transferred into the germlines of mammals through transgenic technology; recombinant-DNA constructs can contain elements from several sources combined in one molecule; and new genetic material could produce important phenotypic changes even in the absence of its expression. Accordingly, the committee chose a nomenclature that would convey the following major categories of genetic modification: (1) the creation of an insertional mutation, (2) the insertion of coding, as opposed to noncoding, elements, and (3) the most important features of the construct as determined by the investigator. For example, in some cases, the coding region of a transgene might be the most relevant factor in the resulting genetic modification; in others, such as insertion of reporter gene constructs, the regulatory apparatus might be the most relevant characteristic.
- *The need to provide a unique identifier for each transgenic strain.* To facilitate identification of each transgenic strain and its source, it is essential that a unique designation conveying such information be part of the strain symbol.
- *The need to develop a nomenclature that can be adapted to species other than mice.* Although almost all existing transgenic animals are mice, transgenic technology can readily be extended to several other species, and transgenic nonmurine mammals, birds, and fish have already been developed. The committee chose to develop a general nomenclature that can be used in all species.

IMPLEMENTATION OF THE NEW NOMENCLATURE

For the nomenclature to contribute to better transgenic-resource management and preservation of transgenic animals, it must first be accepted for use by the major investigators in the field and then be made available to all those developing or using transgenic animals. To achieve the first objective, the committee sent the proposed nomenclature to several major laboratories involved in transgenic research, including two that use species other than the mouse. Comments from those laboratories have been considered in developing the nomenclature.

To achieve the second objective, the committee solicited and has received endorsement of the nomenclature rules from the International Committee on Standardized Genetic Nomenclature for Mice and, in the absence of a functional international nomenclature committee for rats, from the ILAR Committee on Rat Nomenclature. In addition, membership on the present committee of one of the developers of the TADB has allowed us to develop a nomenclature that is compatible with the data base. Promulgation of the nomenclature will simultaneously increase awareness of the existence of the data base.

The committee also identified several other strategies for implementation, including sending the nomenclature for publication in journals that commonly contain papers involving research with transgenic animals and recommending that the editors of the journals make the nomenclature a requirement for acceptance of papers in this field. Moreover, this report has been sent to the categorical institutes of NIH that have an interest in transgenic technology with the request that the rules be provided to the appropriate grantees and contractors and to the study sections that evaluate grant and contract proposals involving transgenic animals.

In the next section, the committee formally proposes its transgene nomenclature. Information on obtaining assistance with naming transgenes or recording transgenes in the data base is contained in Appendix I.

RULES FOR NAMING TRANSGENES

Transgenes are named according to the following conventions.

Symbol

A transgene symbol consists of three parts, all in Roman type, as follows:

$$\text{TgX}(\text{YYYYYY})\#\#\#\#\text{Zzz},$$

where TgX = mode,

(YYYYYY) = insert designation,

\#\#\#\# = laboratory-assigned number, and

Zzz = laboratory code.

Mode. The first part of the symbol always consists of the letters Tg (for "transgene") and a letter designating the mode of insertion of the DNA: N for nonhomologous insertion, R for insertion via infection with a retroviral vector, and H for homologous recombination. The purpose of this designation is to identify it as a symbol for a transgene and to distinguish among three fundamentally different organizations of the introduced sequence relative to the host genome, not simply to indicate the method of insertion or nature of the vector. For example, mice derived by infection of embryos with MULV vectors will be designated TgR, and mice derived by microinjection or electroporation of MULV DNA into zygotes will be designated TgN; mice derived from ES cells by introduction of DNA followed by recombination with the homologous genomic sequence will be designated TgH, while mice derived by insertions of the same sequence by nonhomologous crossing-over events will be designated TgN.

When a targeted mutation introduced by homologous recombination does not involve the insertion of a novel functional sequence, the new mutant allele (often called a "knockout" mutation) will be designated in accordance with the guidelines for gene nomenclature for each species. The gene nomenclature will also be used when the process of homologous recombination results in integration of a novel functional sequence, if that sequence is a functional drug-resistance gene. For example, *Mbpm l D n*, would be used to denote the first targeted mutation of the myelin basic protein (*Mbp*) in the mouse made by Muriel T. Davisson (Dn). In this example, the transgenic insertion, even if it contains a functional neomycin-resistance scene, is incidental to "knocking out" or mutating the targeted locus (see also Lyon, 1989b). The mode symbol TgH is reserved for a time in the future when homologous recombination might be employed to transfer genes to specific sites in the genome using cloned DNA from the target cite to produce a homologous recombination vector. Such target loci might be anonymous, but might exhibit important regulator features that render them desirable for targeting transgenes. A hypothetical example is given on page 50.

Insert designation. The second part of the symbol indicates the salient features of the transgene as determined by the investigator. It is always in parentheses and consists of no more than eight characters: letters (capitals or capitals and lower-case letters) or a combination of letters and numbers. Italics, superscripts, subscripts, internal spaces, and punctuation should not be used. The choice of the insert designation is up to the investigator, but the following guidelines should be used:

- Short symbols (six or fewer characters) are preferred. The total number of characters in the insert designation plus the laboratory-assigned number may not exceed 11 (see below); therefore, if seven or eight characters are used, the number of digits in the laboratory-assigned number will be limited to four or three, respectively.
- The insert designation should identify the inserted sequence and indicate important features. If the insertion uses sequences from a named gene, it is preferable that the insert designation contain the standard symbol for that gene. If the gene symbol would exceed the spaces available, its beginning letters should be used. Hyphens should be omitted when normally hyphenated gene symbols are used. For example, Ins 1 should be used in the symbols of transgenes that contain either coding or regulatory sequences from the mouse insulin gene (*Ins-1*) as an important part of the insert designation. Resources are available to identify standard gene symbols (see Appendix I).
- Symbols that are identical with other named genes in the same species should be avoided. For example, the use of Ins to designate "insertion" would be incorrect.
- For consistency, a series of transgenic animals produced with the same construct might be given the same insert designation. However, that is not required; some lines might manifest unique and important characteristics (e.g., insertional mutations) that would warrant a unique insert designation. If two different symbols are used for the same construct in different transgenic lines, the published descriptions should clearly identify the construct as being the same in both lines. Two different gene constructs used for transgenic animal production, either within a laboratory or in separate laboratories, should not be identified by identical insert designations. Designations can be checked through the available resources (see Appendix I).

- A standard abbreviation can be used as part of the insert designation (see below for an example). If a standard abbreviation is used, it should be placed at the end of the insert. These now include

An (anonymous sequence),
 Ge (genomic clone),
 Im (insertional mutation),
 Nc (noncoding sequence),
 Rp (reporter sequence),
 Sn (synthetic sequence),
 Et (enhancer trap construct), and
 Pt (promoter trap construct).

This list will be expanded as needed and maintained by appropriate international nomenclature committees.

- The insert designation should identify the inserted sequence, not its location or phenotype.

Laboratory-assigned number and laboratory code. The third part of the symbol consists of two components. The laboratory-assigned number is a unique number that is assigned by the laboratory to each stably transmitted insertion when germline transmission is confirmed. As many as five characters (numbers as high as 99,999) may be used; however, the total number of characters in the insert designation plus the laboratory-assigned number may not exceed 11. No two lines generated within one laboratory should have the same assigned number. Unique numbers should be given even to separate lines with the same insert integrated at different positions. The number can have some intralaboratory meaning or simply be a number in a series of transgenes produced by the laboratory. The laboratory code is uniquely assigned to each laboratory that produces transgenic animals. A laboratory that has already been assigned such a code for other genetically defined mice and rats or for DNA loci should use that code. The registry of these codes is maintained by the Institute of Laboratory Animal Resources (ILAR) (see Appendix I).

The complete designation identifies the inserted site, provides a symbol for ease of communication, and supplies a unique identifier to distinguish it from all other insertions. Each insertion retains the same symbol even if it is placed on a different genetic background. Specific lines of animals carrying the insertion should be additionally distinguished by a stock designator preceding the transgene symbol. In general, this designator will follow the established conventions for the naming of strains or stocks of the particular animal used. If the background is a mixture of several strains, stocks, or both, the transgene symbol should be used without a strain or stock name.

Examples

- C57BL/6J-TgN(CD8Ge)23Jwg. The human **CD8** genomic clone (**Ge**) inserted into C57BL/6 mice from the Jackson Laboratory (**J**); the **23rd** mouse screened in a series of microinjections in the laboratory of Jon W. Gordon (**Jwg**).
- Crl:ICR-TgN(SVDhfr)432Jwg. The **SV40** early promoter driving a mouse dihydrofolate reductase (**Dhfr**) gene; **4** kilobase plasmid; the **32nd** animal screened in the laboratory of Jon W. Gordon (**Jwg**). The ICR outbred mice were obtained from Charles River Laboratories (**Crl**).
- TgN(GPDHIm)lBir. The human glycerol phosphate dehydrogenase (**GPDH**) gene inserted into zygotes retrieved from (C57BL/6J x SJL/J)F1 females; the insertion caused an insertional mutation (**Im**) and was the **1st** transgenic mouse named by Edward H. Birkenmeier (**Bir**). No strain designation is provided because each zygote derived from such an F1 hybrid mouse has a different complement of alleles derived from the original inbred parental strains.
- 129/J-TgH(SV4OTk)65Rpw (hypothetical). An **SV40**-thymidine kinase (**Tk**) transgene targeted by homologous recombination to a specific but anonymous locus using embryonic stem cells derived from mouse strain 129/J. This was the **65th** mouse of this series produced by Richard P. Woychik (**Rpw**).

Abbreviations

Transgene symbols can be abbreviated by omitting the insert. For example, the full symbol TgN(GPDHIm)lBir would be abbreviated TgNlBir. The full symbol should be used the first time the transgene is mentioned in a publication; thereafter, the abbreviation may be used.

Insertional Mutations and Phenotypes

The symbol should not be used to identify the specific insertional mutation or phenotype caused directly or indirectly by the transgene. If an insertional mutation that produces an observable phenotype is caused by the insertion, the locus so identified must be named according to standard procedures for the species involved (see Appendix I). The allele of the locus identified by the insertion can then be identified by the abbreviated transgene symbol (see above) according to the conventions adopted for the species.

Examples

- *ho^{TgN447Jwg}*. The insertion of a transgene into the hotfoot locus (*ho*).
- *xxx^{TgN21Jwg}*. The insertion of a transgene that leads to a recessive mutation in a previously unidentified gene. A gene symbol for *xxx* must be obtained from a species-genome data base or member of a nomenclature committee (see Appendix I).

REFERENCES

- Lyon, M. F. 1989a. Nomenclature for transgenic mice. Section 1.2.5 of Rules and guidelines for gene nomenclature. Pp. 10-11 in Genetic Variants and Strains of the Laboratory Mouse, 2d ed., M. F. Lyon, and A. G. Searle, eds. London: Oxford University Press.
- Lyon, M. F. 1989b. Alleles. Section 1.1.5.6 of Rules and guidelines for gene nomenclature. P. 2 in Genetic Variants and Strains of the Laboratory Mouse, 2d ed., M. F. Lyon, and A. G. Searle, eds. London: Oxford University Press.

APPENDIX I

Resources Available for Assistance with Transgenic Nomenclature

Before naming a transgene, an investigator should obtain a laboratory code from ILAR at the address given in the list below. An investigator who has already been assigned such a code for other genetically defined mice and rats or for DNA loci should use the same code. The transgene should be named as stated in the rules. Assistance in selecting transgene symbols is available from several organizations (see below). Lists of named genes for mice and rats are published periodically in *Mouse Genome* (Oxford University Press, Journal Subscriptions Department, Pinkhill House, Southfield Road, Eynsham, Oxford OX8 1JJ, UK) and *Rat News Letter* (Dr. Viktor Stolc, editor, *Rat News Letter*, 2542 Harlo Drive, Allison Park, Pittsburgh, PA 15101). The list of mouse genes is also maintained in GBASE, a genomic data base for the mouse maintained by Dr. Don P. Doolittle, Dr. Alan L. Hillyard, Ms. Lois J. Maltais, Dr. Muriel T. Davisson, Dr. Thomas H. Roderick, and Mr. John N. Guidi at The Jackson Laboratory (see below). Human gene symbols are recorded in the Genome Data Base (GDB), which is maintained at The Johns Hopkins University (see below).

Institute of Laboratory Animal Resources (ILAR). Assigns laboratory codes; assists in naming transgenes; provides rules for naming transgenes. Contact: Dr. Dorothy D. Greenhouse, ILAR, National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418. Tel: 1-202-334-2590; Fax: 1-202-334-1687; Bitnet: DGREENHO@NAS).

The Jackson Laboratory. Assists in naming transgenes; provides rules for standardized nomenclature for mice; provides lists of named mouse genes. Contact: Dr. Muriel T. Davisson, The Jackson Laboratory, Bar Harbor, ME 04609. Tel: 1-207-288-3371; Fax: 1-207-288-8982).

Medical Research Council Radiobiology Unit. Assists in naming transgenes; provides lists of named mouse genes. Contact: Dr. Josephine Peters, MRC Radiobiology Unit, Chilton, Didcot, Oxford OX11 ORD, UK. Tel: 44-235-834-393; Fax: 44-235-834-918.

Transgenic Animal Data Base (TADB). Records, stores, and provides information on transgenic animals, including standardized nomenclature and a complete description of each transgenic animal; maintains rules for transgenic nomenclature on electronic bulletin board. Contact: Ms. Karen Schneider, TADB Coordinator, Oak Ridge National Laboratory, PO Box 2008, MS 6050, Oak Ridge, TN 37831-6050. Tel: 1-615-574-7776; Fax: 1-615-574-9888; Bitnet: TUG@ORNLSTC; Internet: OWENSET@IRAVAX.HSR.ORNL.GOV.

Genome Data Base (GDB). Records, stores, and provides information on mapped human genes and clones. Contact: GDB, Welch Medical Library, The Johns Hopkins University, 1830 East Monument Street, Baltimore, MD 21205. Tel: 1-301-955-9705; Fax: 301-955-0054. For assistance in naming human genes, the contact is Dr. Phyllis J. McAlpine, GDB Nomenclature Editor, University of Manitoba, Department of Human Genetics, 250 Old Basic Sciences Building, 770 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E 0W3. Tel: 1-204-788-6393; Fax: 1-204-786-8712; Bitnet: GENMAP@UOFMCC).

APPENDIX II

The Transgenic Animal Data Base

The [Transgenic Animal Data Base](#) (TADB) is intended to be a comprehensive, online, computerized record of all lines of transgenic animals and animals with targeted mutations that have been generated worldwide. Although the data base now includes only mice, it will be expanded to include other animal species. Transgenic animals of little interest to one researcher might be of enormous interest to others. This situation is addressed through the data base by making available to the scientific community extensive information about transgenic constructs, including methods, expressions, and phenotypes. Standardized nomenclature should be used to enter information into the data base.

Scientists provide data on their own lines of transgenic animals. The TADB office faxes a set of specific questions to each scientist, who answers the questions on a floppy disk with a word-processing program. The floppy disk is returned to the TADB office, where the data are formatted and transferred to the online computer. The result is that pertinent information, published or unpublished, on each line of animals is organized in the data base by the categories listed below. The data base has an easy-to-use, menu-driven interface that enables new users to search for and retrieve relevant records rapidly.

The data base also furnishes an opportunity for users to enter messages to the system administrator. This feature enables the system administrator to assist users who report difficulties and to make necessary adjustments in data base operations to maximize its usefulness. Information on various topics related to use of the data base can be accessed online.

The TADB is stored on an IBM RS6000/320 workstation Server using BRS, a full-text searching software, for retrieval. It is accessible internationally via a toll-free number through the Tymnet telecommunications network. Access through Telnet is also available. Users need a personal computer, a terminal emulation program (such as White Knight, Versaterm, Procom, or Kermit), and a modem to access the data base. Users can get information at no cost from the TADB office. Contact: Ms. Karin Schneider, TADB Coordinator, Oak Ridge National Laboratory, PO Box 2008, MS 6050, Oak Ridge, TN 37831-6050. Tel: 1-615-574-7776; Fax: 1-615-574-9888; Bitnet: TUG@ORNLSTC; Internet: OWENSET@IRAVAX.HSR.ORNL.GOV.

Development of the TADB is sponsored by the National Institute of Environmental Health Sciences, National Institutes of Health, under contract Y01-ES10067.

Categories in the Transgenic Animal Data Base

DOCN	BRS-Assigned Accession Number
DESG	Designation (Standardized Nomenclature) of Transgenic Line
METH	Method Used
DNA	DNA Fragment Introduced
COPY	Copy Number
BACK	Genetic Background of Host Embryo or ES Cells
EXPR	Expression of Transgene or Targeted Gene
PHEN	Phenotype Due to Expression of Transgene or Targeted Gene
INTG	Description of Integration Site
CROS	Crosses with Other Transgenic Lines
IGEN	Genetics of Host Insertional Mutation
ICOM	Comments on Genetics of Host Insertional Mutation
ICLN	Is Flanking Sequence Cloned?
ICHR	Is Mutant Locus Characterized?
IALL	Is Mutation Allelic with Existing Mutations?
IPHN	Phenotype of Insertional Mutation
FCOM	Further Comments Relating to Transgenic Line
MNT	Is Line Being Maintained?
HNDL	Special Handling Instructions for the Animals
QDTE	Is This Line Presently Available to Other Investigators?
CADD	Name and Address of Contact Person
GADD	Name and Address of Author(s) Entering This Record
PUBL	References for Publications Relating to Line
DATE	Date Document Was Entered or Updated



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