# A Mouse by Any Other Name . . .

John P. Sundberg[1,2] and Paul N. Schofield[1,2]

**A recurring motto from the Tony Blair government in the UK was "Education, Education, Education." An appropriate exhortation for the biomedical sciences would be "Standardization, Standardization, Standardization." Inevitably, the two go hand in hand, and the challenge we face is how to encourage researchers to comply with existing or emerging standard terminologies and nomenclatures. This is both an educational and a regulatory task, one in which it is vital to succeed if we are to efficiently and accurately share and use the huge volume of data emerging in the biosciences.**

*Journal of Investigative Dermatology* (2009) **129**, 1599–1601. doi:10.1038/jid.2009.81

Investigators in the fields of medicine and biomedical research communicate effectively, primarily through the use of specialized and defined standard terminology (Becker, 1959; Brown *et al.*, 2007; Friedman, 1955; Jackson, 2001; Porter, 2006; Taylor, 2006). It has remained fluid over time to accommodate new discoveries and technological innovations but remains the key to denoting advances in science. Within the field of dermatology, a committee has functioned for decades to standardize nomenclature (Becker, 1959). The *Journal of Investigative Dermatology* and other publications in the field should insist on strict adherence to the most current dermatological nomenclature to maintain the high esteem of members in the field.

Similar efforts for standardization of nomenclature are currently under way concerning the pathology of the laboratory mouse, now the preeminent model system for human disease (Rosenthal and Brown, 2007). Because this complicated effort covers all organ systems and merges veterinary and human medical terminology, various panels have been formed to address this issue. For cancer, the National Cancer Institute's Mouse Models for Human Cancer Consortium created panels of specialists to review mouse models for human cancer by organ system to develop a consensus nomenclature (http://emice.nci.nih.gov/emice; Cardiff *et al.*, 2000; Kogan *et al.*, 2002; Nikitin *et al.*, 2004; Shappell *et al.*, 2004). A more extensive website, the Mouse Tumor Biology Database (http://tumor.informatics.jax.org), incorporates the mouse genetic literature with images of all types of cancer arising either spontaneously in mice of inbred strains or as a consequence of genetic engineering (Bult *et al.*, 2006; Naf *et al.*, 2002). For general mouse pathology, an international consortium was formed to develop MPATH, an evolving and expanding ontology of mouse pathology terms. The consortium is linked to a large image database (http://www.Pathbase.net). These online resources are supplemented by highly specialized residential training courses and internship programs (Sundberg *et al.*, 2007), but even with these opportunities, a significant gap remains between demand and availability of appropriately trained pathologists (Schofield *et al.*, 2009).

The second annual meeting of Coordination and Sustainability of International Mouse Informatics Resources (http://www.casimir.org.uk), held at the Nobel Forum, Stockholm, Sweden, 2–3 December 2008, focused on the topic "One Medicine, One Pathology," with the goal of coordinating data collection, nomenclature, and comparative pathology among various disciplines (Sundberg and Schofield, in press). These approaches refine existing nomenclature systems developed over the previous two centuries, with which all medically trained scientists are familiar. Researchers should use these online resources to double-check interpretations and standardize the results described in their publications. To that end, databases are now available that provide a "virtual second opinion" for mouse pathology nomenclature, with links to photomicrographs (http://research.jax.org/faculty/sundberg/index.html; Sundberg *et al.*, in press; Sundberg *et al.*, 2008).

A larger and far more serious nomenclature issue involves genetic terminology, an area in which few have been trained. Rules for genetic nomenclature were devised in 1919, when the American Society of Naturalists appointed a Committee on Genetic Form and Nomenclature, with CC Little as chairman (Little, 1921). As they applied to the mouse, these rules were published in 1940 by Dunn, Grueneberg, and Snell (Dunn *et al.*, 1940). Subsequently, the International Committee for Standardized Genetic Nomenclature in Mice (Green *et al.*, 1963) was formed to standardize nomenclature for inbred, congenic, and recombinant inbred strains as well as mutant locus/gene symbols. Investigators proposed new names for mutant mouse strains and stocks (and later for genes) to this committee, and unique names and symbols were assigned to prevent ambiguity. Unfortunately, journal editors have been slow to require authors to adhere to this system, creating major problems. Today, with the advent of genetic engineering and large-scale mutagenesis projects, multiple allelic mutations (both spontaneous or chemical/radiation-induced "remutations" and multiple constructs of targeted mutations involving the same gene), often with very different phenotypes, are available. Strain and mutation symbols, when used correctly, are critical to the materials and methods section of any manuscript, and

[1]*The Jackson Laboratory, Bar Harbor, Maine, USA and* [2]*Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK*

*Correspondence: Dr John P. Sundberg, The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609, USA. E-mail: john.sundberg@jax.org*

they help reviewers determine which allelic mutation is under investigation, enabling them to determine the validity of the work being reported.

Mouse (International Committee on Standardized Genetic Nomenclature for Mice: http://www.informatics.jax.org/mgihome/nomen/strains.shtml), human (HUGO Gene Nomenclature Committee: http://www.genenames.org), and rat (Rat Gene Nomenclature Committee: http://rgnc.gen.gu.se/RGNChem.html) nomenclature rules are available online. For laboratory mice, names of inbred strains are in all capital letters. After a forward slash (/) following the strain name, and equally important, are the laboratory (investigator) and institutional codes that designate substrains. For example, NOD/ShiLtSzJ designates a subline of the nonobese diabetic strain originally inbred at Shionogi (Shi), in Japan, and later maintained by Edward Leiter (Lt), from whose colony a subline was initiated by Leonard Shultz (Sz). The strain is maintained and distributed by The Jackson Laboratory (J). Abbreviations for commonly used inbred strains are also standardized. C57BL/6J is abbreviated B6, which is also used to refer to mixed or unknown/unspecified C57BL/6 substrains. B6ByJ refers to C57BL/6ByJ and B6EiJ to C57BL/6JEi, which, like many other substrains, carry unique mutations. In contrast, the BALB/cJ inbred strain is abbreviated C, and BALB/cByJ mice are CBy.

Mixed inbred or incipient congenic strains, in which a mutated gene is being transferred from one strain background onto another strain, are designated by a semicolon between the strain abbreviations (e.g., B6;129), followed by a hyphen and the mutant gene symbol. This nomenclature, indicating a segregating background, is in sharp contrast to congenic strain names, in which the semicolon is replaced by a period to indicate that the congenic procedure has been completed (10 backcrosses, N10, onto the new strain, e.g., B6.129). Six backcross generations (N6; incipient congenic) are commonly accepted by many journals as adequate, and many mouse distributors use congenic nomenclature at N5; however, speed congenic technology has demonstrated that this is not optimal (Markel *et al.*, 1997).

Mouse gene symbols are shown in italics with only the first letter capitalized. Symbols for dominant or semidominant spontaneous or chemical/radiation-induced mutations of unidentified genes are written in the same manner as gene symbols. Recessive allelic mutations appear entirely in lowercase. Once the previously unknown gene has been identified, the allele (mutation) symbol is superscripted, appearing immediately after the gene symbol. For example, the mouse hairless and rhino Jackson mutations are written $Hr^{hr}$ and $Hr^{rh7J}$, respectively. To differentiate them from mouse genes, human gene symbols are presented in all capital letters; e.g., the human hairless gene symbol is *HR*. For both mice and humans, gene and allele names (as opposed to symbols) are written entirely in lowercase unless they include a proper noun, as with Alstrom syndrome I. Whereas gene symbols are italicized, symbols for their respective proteins are not. The symbols for both mouse and human proteins are printed entirely in capital letters.

> Use of standardized genetic nomenclature is absolutely essential

Specific nomenclature guidance for strains, genes, alleles/mutations, and chromosomal aberrations can be found on the Mouse Genome Informatics website via links from the Nomenclature Home Page (http://www.informatics.jax.org/mgihome/nomen/gene.shtml). Strict adherence to these nomenclature standards will allow work to be compared fairly and, more important, reviewed accurately.

The power of informatics to integrate and analyze phenotype and genotype data within and across species is continually increasing, although it is still outstripped by the volume of emerging data, particularly from the analysis of mouse mutants. It is essential that the way in which alleles are expressed and disease descriptions are captured be semantically unambiguous and standardized to allow computational analysis. Nonstandard nomenclature is a serious barrier to the analysis of large historical datasets in which local nomenclature and data structure are idiosyncratic. In addition, it is becoming a rate-limiting step in the analysis of new data, particularly data published only in the printed literature and not uploaded to databases, because failure to use standardized terminology results in ambiguity and inaccuracy, which confound text-mining tools, resulting in the need for laborious and expensive extraction of the data by professional curators.

## CONFLICT OF INTEREST

The authors state no conflict of interest.

## ACKNOWLEDGMENTS

We thank Beverly Richards-Smith for her constructive comments and verification of nomenclature issues raised in the manuscript. This work was supported by grants from the National Institutes of Health (CA34196, CA089713, and RR17436) and the Commission of the European Community, Framework Programme 6 Contract LSHG-CT-2006-037811, CASIMIR.

## REFERENCES

Becker SW (1959) Dermatological nomenclature. *Arch Derm* 80:778–87

Brown SJ, Tilli CMLJ, Jackson B, Avilion AA, MacLeod MC, Maltais LJ *et al.* (2007) Rodent *Lce* gene clusters; new nomenclature, gene organization, and divergence of human and rodent genes. *J Invest Dermatol* 127:1782–6

Bult CJ, Krupke DM, Vincent MJ, Allio T, Sundberg JP, Mikaelian I *et al.* (2006) The Mouse Tumor Biology Database: an online resource for mouse models of human cancer. In: Nagel S (ed) *Cancer Bioinformatics: From Therapy Design to Treatment*. Wiley: West Sussex, UK, 143–53

Cardiff RD, Moghanaki D, Jensen RA (2000) Genetically engineered mouse models of mammary intraepithelial neoplasia. *J Mammary Gland Biol Neoplasia* 5:421–37

Dunn LC, Grüneberg H, Snell GD (1940) Report on the committee of mouse genetics nomenclature. *J Hered* 31:505–6

Friedman AA (1955) Medical nomenclature and dermatology. *Va Med Mon (1918)* 82:516

Green MC, Grueneberg H, Hertwig P, Heston WE, Lyon MF, Medvedev NN *et al.* (1963) A revision of the standardized genetic nomenclature for mice. *J Hered* 54:159–62

Jackson R (2001) What's in a name? Comments on the Dermatological Dictionary by Ledier, Rosenblum, and Carter. *J Cutan Med Surg* 5:505–7

Kogan SC, Ward JM, Anver MR, Berman JJ, Brayton C, Cardiff RD *et al.* (2002) Bethesda proposals for classification of nonlymphoid hematopoietic neoplasms in mice. *Blood* 100:238–45

Little CC (1921) Report of the Committee on Genetic Form and Nomenclature. *Am Nat* 55:175

Markel P, Shu P, Ebeling C, Carlson GA, Nagle DL, Smutko JS *et al.* (1997) Theoretical and empirical issues for marker-assisted breeding of congenic mouse strains. *Nat Genet* 17:280–4

Naf D, Krupke DM, Sundberg JP, Eppig JT, Bult CJ (2002) The mouse tumor biology database: a public resource for cancer genetics and pathology of the mouse. *Cancer Res* 62:1235–40

Nikitin A, Alcaraz A, Anver MR, Bronson RT, Cardiff RD, Dixon D *et al.* (2004) Classification of proliferative pulmonary lesions of the mouse: recommendations of the mouse models of human cancers consortium. *Cancer Res* 64:2307–16

Porter RM (2006) The new keratin nomenclature. *J Invest Dermatol* 126:2366–8

Rosenthal N, Brown S (2007) The mouse ascending: perspectives for human-disease models. *Nat Cell Biol* 9:993–9

Schofield PN, Brown SD, Sundberg JP, Arends M, Warren MV, Dubus P *et al.* (2009) PRIME importance of pathology expertise. *Nat Biotechnol* 27:24–5

Shappell SB, Thomas GV, Roberts RL, Herbert R, Ittmann MM, Rubin MA *et al.* (2004) Prostate pathology of genetically engineered mice: definitions and classification. The consensus report from the Bar Harbor meeting of the Mouse Models of Human Cancer Consortium Prostate Pathology Committee. *Cancer Res* 64:2270–305

Sundberg JP, Schofield PN (in press) One medicine, one pathology, one health concept. *J Am Vet Med Assoc*

Sundberg JP, Hackman RC, HogenEsch H, Nikitin AY, Ward JM (2007) Training mouse pathologists: Five years of Pathology of Mouse Models of Human Disease Workshops. *Toxicol Pathol* 35:447–8

Sundberg JP, Sundberg BA, Schofield PN (2008) Integrating mouse anatomy and pathology ontologies into a diagnostic/phenotyping database: tools for record keeping and teaching. *Mammalian Genome* 19:413–9

Sundberg BA, Schofield PN, Gruenberger M, Sundberg JP (in press) A data capture tool for mouse pathology phenotyping. *Vet Pathol*

Taylor S (2006) As simple as black and white? *J Am Acad Dermatol* 54:1070–1

*See related article on pg 1643*

# Complexity of the Association Between Psoriasis and Comorbidities

Tamar Nijsten[1] and Marlies Wakkee[1]

**Multiple observational studies have recently demonstrated associations between psoriasis and several comorbidities—especially metabolic syndrome and cardiovascular disease, and now osteoporosis. It has been hypothesized that elevated levels of tumor necrosis factor-α are a biological explanation for the observed associations. In this commentary, we discuss the complexity of associations between psoriasis and comorbidities, possible residual confounding, the limitations of observational studies in proving causality, absolute versus relative risk differences, and the clinical relevance and possible clinical impact of "upgrading" psoriasis to a systemic disease.**

*Journal of Investigative Dermatology* (2009) **129**, 1601–1603. doi:10.1038/jid.2009.55

Several observational studies have recently demonstrated that psoriasis is associated with diseases other than psoriatic arthritis, including cardiovascular disease and metabolic syndrome, cancer, chronic obstructive pulmonary disease, depression, and, in this issue, osteoporosis (Mallbris *et al.*, 2004; Gelfand *et al.*, 2006a,b; Dreiher *et al.*, 2008a,b). The trend in scientific literature and meeting presentations has been to "upgrade" psoriasis from a cutaneous to a systemic disease. But before we consider accepting this hypothesis, which may have a considerable impact on the management of patients, the limitations of observational study designs and the available evidence should be reviewed.

[1]*Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands*

*Correspondence: Dr Tamar Nijsten, Department of Dermatology, Erasmus MC, Burg. s' Jacobsplein 51, 3015 CA Rotterdam, The Netherlands. E-mail: t.nijsten@erasmusmc.nl*

## Complexity of association

The direct link between psoriasis and many of the possibly associated diseases is the presence of chronic inflammation and, in particular, elevated levels of the multifunctional cytokine tumor necrosis factor-α . However, several other factors may play important roles and confound this association (Figure 1). First, psoriasis has a major impact on patients' lives and is associated with depressive symptoms in a relatively large proportion of patients (Stern *et al.*, 2004). Impaired health-related quality of life (HRQOL) may lead to unhealthy lifestyle behaviors such as smoking, alcohol consumption, decreased physical activity, and obesity, which are independent risk factors for many other diseases. Conversely, obesity and smoking may increase the risk of developing psoriasis (Naldi *et al.*, 2005; Setty *et al.*, 2007), suggesting that these may be primary risk factors for several comorbidities and that psoriasis is no more than an innocent bystander. The presence of psoriatic arthritis may further limit patients' physical functioning. In addition, psoriasis therapies (e.g., cyclosporine and prolonged topical steroid use) may increase the risk of several comorbidities (e.g., cardiovascular risk and osteoporosis, respectively), and other drugs used to treat comorbidities may induce or exacerbate psoriasis (e.g., β-blockers and lithium). In addition to HRQOL impairment and (prior) drug exposure, several epidemiological biases may affect the association.

Most importantly, psoriasis patients are more likely to visit physicians because of their disease than "healthy" people from the general population, which puts them at risk for being screened for and diagnosed with other diseases. This detection bias is especially important in the diagnosis of common diseases that are typically underdiagnosed, such as hypertension and osteoporosis in men (Dreiher *et al.*, 2008a). Moreover, most psoriasis patients have limited disease (affecting less than one palm-sized area; Stern *et al.*, 2004), and patients who seek medical care for their limited psoriasis are probably also more likely to seek care sooner for