DOI:10.1111/j.1600-0625.2008.00751.x
www.blackwellpublishing.com/EXD

Animal models of psoriasis: a critical appraisal

Michael P. Schön

Department of Dermatology, University of Göttingen, Göttingen, Germany
Correspondence: Prof. Dr. Michael P. Schön, Department of Dermatology and Venereology, University of Göttingen, Von-Siebold-Str. 3, 37075 Göttingen, Germany, Tel.: +49551396401, Fax: +49551396841, e-mail: michael.schoen@med.uni-goettingen.de

Accepted for publication 9 April 2008

Abstract: Although there is no naturally occurring disorder in laboratory animals that mimics the complex phenotype of psoriasis, a large number of spontaneous or genetically engineered mutations in rodents, immunological reconstitution approaches or xenotransplantation models have shed light on specific aspects implicated in the pathophysiology and therapy of psoriasis. Animal models have helped to elucidate functions of inflammatory mediators or to unravel the contribution of innate or adaptive immune mechanisms, keratinocytes or endothelial cells to chronic hyperproliferative inflammatory skin disorders. However, given that several distinct manipulations of molecular pathways, resident cutaneous cell types or immigrating immunocytes result in remarkably similar phenotypes in experimental animals, it appears that interfering with cutaneous homeostasis in general may ultimately initiate a rather uniform reaction pattern that mirrors some features of psoriasis. This limitation of animal models generated without the use of human material may, at least in part, be overcome by xenotransplantation of human skin onto immunocompromised animals. The latter approach has been employed in preclinical investigations to study the role of immune cells and/or to predict the efficacy of some therapeutic compounds. This brief review delineates approaches to generate animal models of psoriasis and discusses their strengths and limitations for psoriasis research.

Key words: animal models – psoriasis – skin inflammation – transgenic mouse

Please cite this paper as: Animal models of psoriasis: a critical appraisal. Experimental Dermatology 2008; 17: 703–712.

Setting the stage

Psoriasis is a very popular disease among skin researchers. A quick glance at publications related to the pathogenesis of psoriasis over the past four decades may suffice here to substantiate this notion (more than 11 000 papers published from 1965 to 2007 with an ever-increasing tendency; Fig. 1a). Having stated this, one may be somewhat surprised to find a number of central questions in psoriasis research not conclusively answered yet. For example, we still do not have a comprehensive notion on the relative contributions of resident cutaneous cells versus immigrating immune cells, and even the relative importance of subsets of immunocytes (i.e. innate versus adaptive immunity) in the disease process is not entirely clear yet (1–4). Likewise, although several psoriasis susceptibility loci have been identified in the last decade, the genetic basis of psoriasis is still not completely understood (5–7).

In this situation, experimental animal models that mimic the human disease would come in very handy with respect to both researches into the pathogenesis of psoriasis and drug development. However, despite decades of devoted research an animal model that completely resembles the complex human disease without the use of human material, as opposed to animal models, which are based on transplantation of human tissue or cells, is not yet available (8,9). At least three aspects generally inherent to complex disorders, which are not mutually exclusive, may be considered as explanations for this situation: the first obvious approach to generate an animal model of psoriasis is to somehow tamper with normal skin through targeting of a key molecule or cell type to induce the desired pathological alterations. However, it appears that there is no single feature that is truly unique to psoriasis, for example, metabolic and biochemical abnormalities are found in psoriasis and other inflammatory skin disorders, dysregulation of any given inflammatory mediator or adhesion molecule may also be found in diseases unrelated to psoriasis, genetic markers show only statistical associations with psoriasis, and established therapies are not exclusively effective in psoriasis. Thus, identifying the right candidate target molecules or cells within a plethora of intertwined factors appears difficult, if possible at all. Second, the alternative or complementary approach would be to specifically eliminate (target) candidate cells or mediators in animal models in order to identify crucial elements of the pathogenic cascade. However, as outlined below, this approach also bears some imponderable challenges, as targeting different molecules or cells in a given model may similarly influence the phenotype and, therefore, may not convincingly allow

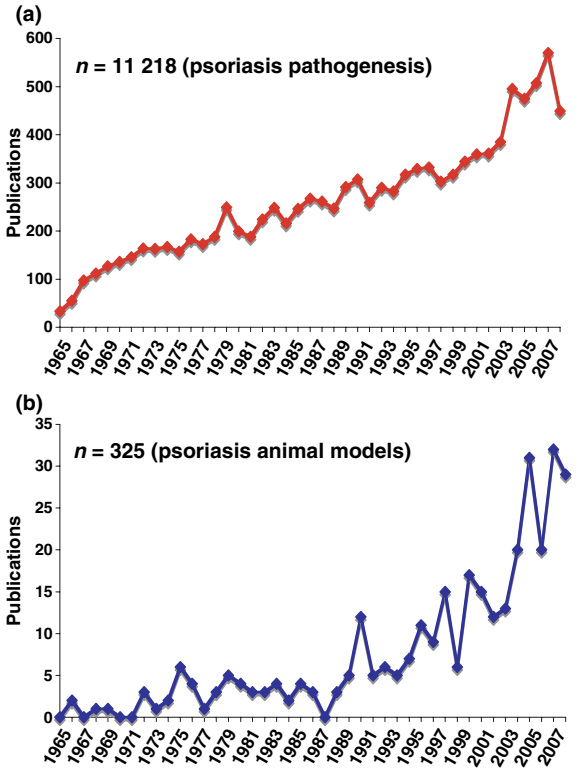

Figure 1. Publications related to the pathogenesis of psoriasis (a) and animal models of psoriasis (b) (resulting from a Medline search in November 2007) show consistently increasing numbers over the past four decades.

identifying the primary pathogenic components. Finally, with the possible exception of a few anecdotal reports on spontaneously occurring conditions with psoriasis-like features in some non-human primates, dogs and pigs (10–13), which occurred sporadically, thus precluding systematic investigations, there is no known naturally occurring disorder in non-human species that exhibits all of the pathologic alterations seen in psoriasis (i.e. chronic inflammatory erythrosquamous skin lesions underlied by epidermal hyperproliferation, altered differentiation, angiogenesis and a psoriasis-like infiltrate) and which responds to antipsoriatic therapy. It is, therefore, not easy to predefine the setting in which psoriasis can be studied successfully in an animal model.

Approaches to mimic features of psoriasis in animal models

Despite the aforementioned *a priori* challenges, many publications (whose numbers are steadily increasing; Fig. 1b) have addressed psoriasis-related issues in animal models during the past four decades. On one hand, these approaches have vastly increased our understanding of various mechanisms of chronic inflammation, which are thought to be relevant for psoriasis. On the other hand, they also highlight some as yet unresolved issues in psoriasis research, e.g. the contribution of the epidermis/keratinocytes, innate and adaptive immunity to the pathogenesis of psoriasis and to drug development. However, as discussed below, such models may ultimately not suffice to resolve those issues. There are several principle approaches to animal models of psoriasis whose specifics have been extensively reviewed (8,9).

Spontaneous mutations

The first psoriasis models described were spontaneous mutations in mice, which are associated with a more or less psoriasis-like phenotype on certain genetic backgrounds and allelic mutations. Spontaneous mutations with a psoriasiform phenotype include mice homozygous for the asebia ($Scd1^{ab}/Scd1^{ab}$) (14), chronic proliferative dermatitis ($Sharpin^{cpdm}/Sharpin^{cpdm}$) (15,16) and the flaky skin ($Ttc7^{fsn}/Ttc7^{fsn}$) mutation (17,18). The asebia mouse mutation exhibits moderate epidermal acanthosis, increased dermal vascularity and a dermal infiltrate composed of macrophages and mast cells, but neither T cells nor neutrophils. In contrast, both chronic proliferative dermatitis and flaky skin mice exhibit epidermal hyperproliferation, a mixed inflammatory infiltrate with neutrophils accumulating in epidermal microabscesses, and increased dermal vascularity with dilated blood vessels. Backcrosses to different mouse strains suggested that several modifier genes affect the phenotype, including the composition of the inflammatory infiltrate. The flaky skin phenotype is very complex and comprises aspects not present in psoriasis. The $Sharpin^{cpdm}/Sharpin^{cpdm}$ mutation results in a similarly complex phenotype, affecting several organ systems. Both phenotypes, chronic proliferative dermatitis and flaky skin, appear to develop independent of T cells, and both disorders do not respond adequately to some antipsoriatic therapies (19–21).

Genetically engineered animals

More specific genotype–phenotype studies can be performed in transgenic animals. This approach has been employed to investigate the role of numerous adhesion molecules, cytokines, transcription factors and other mediators in the pathogenesis of hyperproliferative inflammatory skin disorders. A frequently used approach is epidermal overexpression of molecules of interest under the control of promoters acting in basal (e.g. keratin 14) or suprabasal keratinocytes (e.g. involucrin or keratin 10). Among the target molecules studied in such transgenic approaches are transforming growth factor (TGF)-α (22), interleukin (IL)-6 (23), keratinocyte growth factor (KGF) (24), IL-1α (25), latent human TGFβ (26), vascular endothelial growth

factor (VEGF) (27,28), interferon (IFN)-γ (29), bone morphogenic protein (BMP)-6 (30), the angiogenesis-related Tie2 (31), amphiregulin (32), p40 (the common subunit of the proinflammatory cytokines IL-12 and IL-23) (33,34), IL-20 (35), collagenase (36), MEK1 (a MAP kinase upstream of Erk) (37), or human α_2, α_5 and β_1 integrin subunits (38). The opposite strategy, i.e. deletion (or diminution) of putative key molecules, was followed to study leukocyte β_2 integrins (CD18) (in a hypomorphic mutation in PL/J mice) (39), IL-1ra (40), IRF-2 (41) or integrin α_E (42). In addition, the role of signal transduction in psoriasiform skin inflammation was studied by deleting the inhibitor of nuclear factor (NF)-κB-kinase 2 (IKK2) (43), signal transducer and activator of transcription 3 (Stat3) (44), or Jun proteins (45) within the epidermis.

Immunological approaches

Based on the assumption that immune mechanisms underlie the pathogenesis of human psoriasis, several rodent models have focused on primary immunological manipulations to generate psoriasiform phenotypes. Along this line, adoptive transfer of $CD4^+$ T cells from human HLA-B27/β2m-transgenic rats (46) into non-transgenic immunocompromised rats (*Foxn1*^{rnu}/*Foxn1*^{rnu}) was sufficient to induce psoriasis-like skin alterations in the recipients (47). In addition, a psoriasiform disorder was observed in *Prkdc*^{scid} mice receiving $CD4^+$/$CD45RB^{hi}$ T cells from major histocompatibility complex (MHC)-matched, but minor histocompatibility mismatched donors (48,49). Recombinase activating gene (*Rag*)-*2*-deficient mice reconstituted with $CD4^+$/$CD45RB^{hi}$ T cells developed a similar phenotype (50), indicating that psoriasiform skin lesions can, in principle, be induced by T cells alone.

Strengths and weaknesses of animal models of psoriasis

A number of important questions in psoriasis research have been addressed by the above mentioned rodent models, and the authors of the respective papers usually conclude that their findings may contribute to the resolution of important issues in the human disease. Few such questions have been outlined briefly.

Epidermal pathogenesis of psoriasis?

The decade-long discussion whether the epidermal alterations observed in psoriasis are cause or consequence of the chronic inflammation (51) has been fuelled prominently by animal models. However, as exemplified by some selected models, the results appear to be somewhat disparate: when mice overexpressing IL-6 (23), KGF (24) or TGFα (22) under the control of the keratin 14 promoter were studied, keratinocyte proliferation and differentiation, inflammatory cells or angiogenesis within the skin were found to be affected either not at all or only marginally. When IL-1α was assessed in a similar way, chronic inflammatory lesions were occasionally observed depending on the level of transgene expression (25), while involucrin promoter-driven expression of IFNγ resulted in epidermal hyperproliferation, enlarged dermal capillaries, and induction of MHC class II and intercellular adhesion molecule (ICAM)-1 (29). However, no amelioration of cutaneous inflammation was observed in IFNγ-deficient mice in a more recent study (52). Transgenic mice with low levels and patchy expression of BMP-6 exhibit marked epidermal hyperproliferation along with an inflammatory infiltrate, including epidermal microabscesses (30). The phenotype of mice expressing some human β1-integrins within the suprabasal epidermis (controlled by the involucrin promoter) resembled psoriasis in several aspects, including epidermal recruitment of $CD8^+$ T cells (38). Some recent studies indicate that altered signal transduction within keratinocytes may cause a psoriasis-like phenotype in mice: mice with an epidermis-specific deletion of inhibitor of NF-κB kinase 2 (IKK2) develop a T cell-independent, psoriasis-like skin disease (43). Another study highlights the importance of JunB, the expression of which is substantially reduced in lesional psoriatic skin. C-Jun, a proposed antagonist of JunB, shows the opposite expression pattern in psoriasis (45) as well as in some hyperproliferative skin disorders in mice, such as the psoriasiform disease caused by reconstitution of *Prkdc*^{scid} mice with $CD4^+$/$CD45RB^{hi}$ T cells (Fig. 2) (49). It was found that mice lacking either gene alone showed a normal phenotype, whereas double knockout mice exhibited a psoriasis-like skin disease. Finally, when Stat3 was constitutively active within the epidermis of mice, a chronic hyperproliferative inflammatory skin disorder developed. However, this psoriasis-like disorder was dependent on T lymphocytes (44).

Pathogenic role of the cutaneous vasculature?

Increased and altered vascularisation and angiogenesis, which is an integral part of the psoriatic phenotype, is featured by several of the spontaneous or genetically engineered mutant rodents as part of their inflammatory phenotype. Again, transgenic approaches were taken to clarify whether angiogenesis-related factors were sufficient to initiate psoriasiform inflammation. Indeed, targeting expression of VEGF to the epidermis resulted in some psoriasis-like features (27,28). In addition, transgenic mice overexpressing Tie-2 stimulating cutaneous angiogenesis exhibit a chronic hyperproliferative inflammatory skin phenotype (31).

Therefore, some of the animal models mentioned thus far support the hypothesis that under certain conditions,

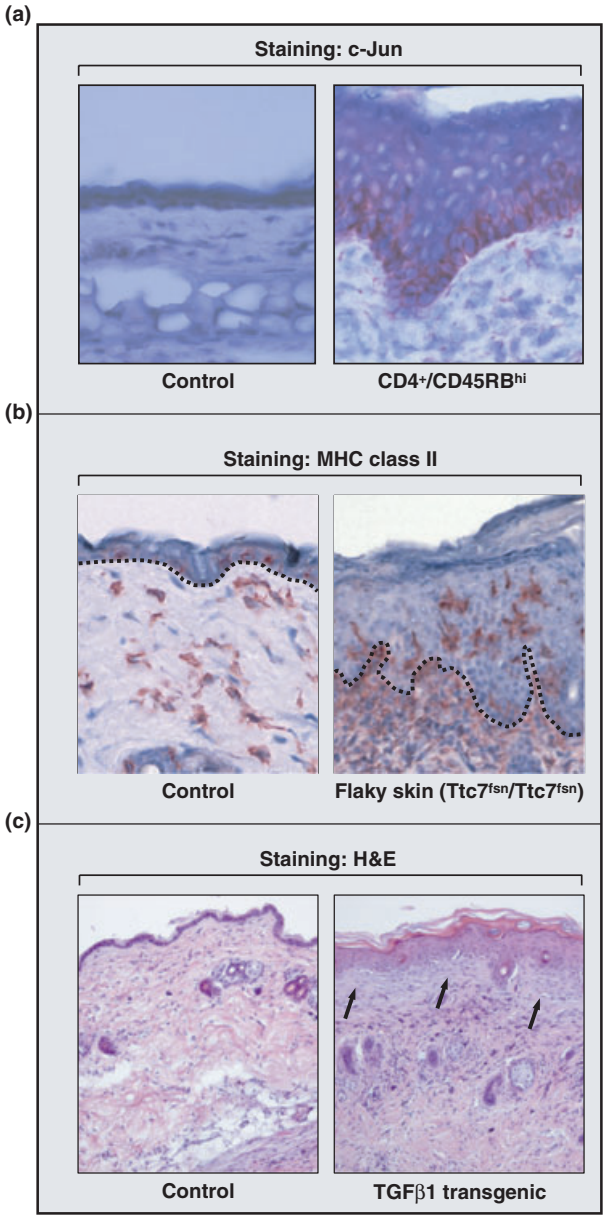

Figure 2. Similarities and differences of animal models compared with human psoriasis. The immunocompromised recipients of $CD4^+/CD45RB^{hi}$ T lymphocytes (a), flaky skin mice (b) and transgenic mice with epidermal expression of latent TGFβ1 (c) all show a hyperproliferative inflammatory cutaneous phenotype displaying some features of human psoriasis. The examples shown highlight that some features are shared between human psoriasis and certain animal models [e.g. epidermal induction of c-Jun in (a)], while others may differ, such as the lacking induction of MHC class II on keratinocytes [only epidermal Langerhans cells are MHC class II positive in flaky skin mice; the dashed lines indicate the location of the dermo-epidermal junction; (b)] or the development of fibrosis in the TGFβ1-transgenic mice [indicated by arrows in (c)].

primary cutaneous abnormalities (either within the epidermis or the vascular system) are sufficient to initiate a pathogenic cascade, leading to a psoriasis-like phenotype. However, while important insights into the *in vivo* action of such key molecules within the skin have been gained, tampering with a single cytokine or adhesion molecule apparently did not elicit the complete phenotype of psoriasis, thus supporting the notion of a cytokine network instead (53). In addition, all of the phenotypes mentioned thus far resulted from aberrant expression of gene products within the epidermis, a possibly relevant factor that will be discussed below.

Adaptive immunity and psoriasis?

A substantial body of clinical and experimental evidence suggests that T cells are key effectors in psoriasis (1,2,4). Indeed, adoptive transfer of T cells was sufficient in some animal models to induce a psoriasis-like skin disorder without primary epithelial abnormalities: transgenic expression of human HLA-B27/β2m in rats resulted in psoriasiform skin changes and arthritis in a subset of animals (46). However, transfer of $CD4^+$ T cells from these animals into non-transgenic $Foxn1^{rnu}/Foxn1^{rnu}$ rats was sufficient to induce psoriasiform skin alterations in the recipients (47). In addition, induction of a psoriasis-like phenotype was achieved in immunodeficient mice receiving $CD4^+/CD45RB^{hi}$ T cells from MHC-matched, but minor histocompatibility mismatched donors (49). Similar to psoriasis, IL-12 and IFNγ appear to be important for the pathogenesis of the chronic skin inflammation in this model (48), and the principle has been confirmed later in other immunodeficient recipients, i.e. *Rag-2*-deficient mice (50). This phenotype responded to immunosuppressive therapies and was suppressed by $CD4^+/CD45RB^{lo}$ T cells, indicating that psoriasis-like skin lesions can, in principle, be evoked through T cell dysregulations in the absence of primary cutaneous abnormalities. However, as detailed below, the penetrance of the chronic inflammatory phenotype is variable in these models and, although T cells are involved, the models have not led to the identification of a putative antigen.

Pathogenic role of innate immunity?

A role of the innate immune system in the pathogenesis of psoriasis is suggested not only by several lines of experimental evidence (54) but also by the clinical efficacy of compounds inhibiting tumor necrosis factor (TNF)α, a primary cytokine linking functions of innate and adaptive immunity (55). Indeed, some animal models appear to corroborate the notion that components of the innate immune system contribute prominently to the pathogenesis of psoriasiform lesions: the skin lesions of CD18 hypomorphic mice ($Itgb2^{tm1Bay}/Itgb2^{tm1Bay}$ on the PL/J strain) contain large numbers of TNF-producing macrophages (39). Neutralising TNF or macrophage depletion in these mice resulted in alleviation of the inflammatory skin disorder

(56). T cells, neutrophils, mast cells or Langerhans cells were not affected by macrophage depletion. Given that the psoriasis-like phenotype was only obtained after combined injection of monocyte chemoattractant protein 1 (MCP-1) and TNFα into unaffected skin, but not by either mediator alone, both cutaneous recruitment and subsequent activation of macrophages into the skin appeared to be necessary for disease development (56). Similar results were obtained when the role of macrophages was assessed in mice with epidermis-specific deletion of IKK2 (43,52), suggesting that interference with macrophage functions may be a common denominator in some mouse models of chronic hyperproliferative skin disorders, independent of their way of generation. It has been concluded that dermal macrophages, once activated through various triggers, produce large amounts of TNF, ultimately sustaining a vicious circle resulting in psoriasis-like transformation of the skin. Again, these observations have been extrapolated to human psoriasis (57).

In flaky skin mice, a phenotype that may develop in the absence of a functional adaptive immune system (20), a pathogenic role of neutrophils for the generation of the skin symptoms has been suggested based on antibody-mediated depletion (58). In contrast, neutrophil depletion in CD18 hypomorphic mice ($Itgb2^{tm1Bay}/Itgb2^{tm1Bay}$ on the PL/J strain) did not alleviate inflammation (56). It appears, therefore, that at least some aspects regarding the role of innate immune mechanisms are discrepant between certain animal models, and the transferability of the respective mechanisms to the human disease awaits further investigations.

Uniform cutaneous reaction patterns in animal models of psoriasis

All of the above mentioned approaches represent animal models with more or less psoriasis-like cutaneous features whose phenotypes and putative pathogeneses have been reviewed extensively (8,9). However, considering the diversity of targeted structures primarily affected in these spontaneously mutated, genetically engineered or immunologically manipulated rodents, which have been published as models for psoriasis, it appears that very similar hyperproliferative inflammatory phenotypes can be obtained through many diverse approaches (examples depicted in Fig. 2). For example, many genetically engineered animals with targeted mutations within the epidermis, the vasculature or immune cells exhibit chronic hyperproliferative inflammatory skin changes. Similar phenotypes may occur in spontaneous mutations or immunological transfer models, although some aspects may vary (such as dermal fibrosis in TGFβ1-transgenic mice or lacking induction of MHC class II in flaky skin mice, Fig. 2). Thus, the mere generation of such models may not suffice to identify cells or mediators that are crucial initiators of psoriatic skin lesions in humans, if that is possible at all.

The complementary approach, i.e. specific elimination (targeting) of candidate cells or mediators in animal models to identify crucial elements of the pathogenic cascade may also not be sufficient to conclusively identify initiators of the pathogenesis of psoriasis, as exemplified by CD18 hypomorphic mice ($Itgb2^{tm1Bay}/Itgb2^{tm1Bay}$ on the PL/J strain) where either depletion of T cells (59) or macrophages (56) resulted in alleviation of the psoriasiform phenotype.

To some degree, it appears that perturbations of the cutaneous homeostasis at (almost) any point may result in a chronic inflammatory phenotype that may – sales-promotional to some extent – be called psoriasis-like or psoriasiform (some examples are schematically depicted in Fig. 3). As evidenced by several examples, genes whose expression is targeted to the basal layers of the epidermis appear to be particularly prone to lead to an inflammatory hyperproliferative phenotype. Thus, animal models have not yet answered the central question in psoriasis research, namely whether psoriasis is based on an intrinsic defect

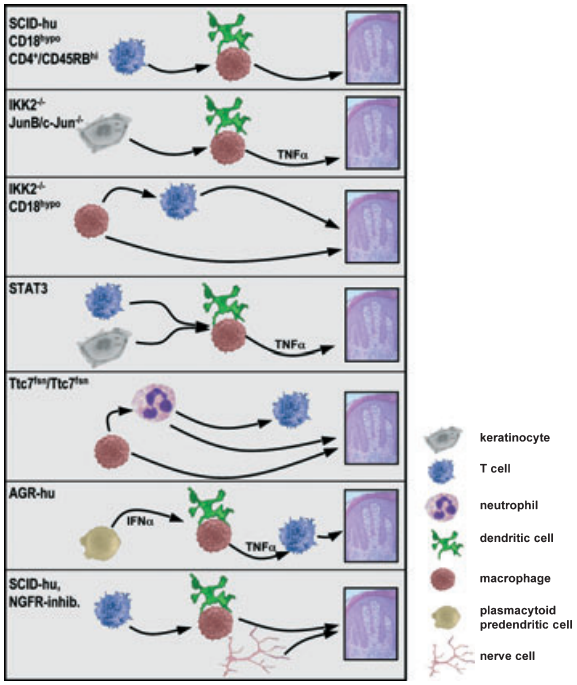

Figure 3. Synopsis of selected pathogenic concepts of psoriasis supported by animal models. As detailed in the text, rather diverse manipulations of the cutaneous homeostasis may result in chronic inflammatory hyperproliferative skin lesions. Depending on the model used – some examples are listed in the panels – tampering with different cell types or molecular functions trigger the development of hyperproliferative inflammatory skin changes, suggesting different pathogenic mechanisms.

within the skin or is a primary autoimmunological disorder. Further along this line, if psoriasis is indeed a disorder with an immunological basis (our currently favoured notion), then there are some experimental systems highlighting the primary importance of the adaptive immune system (i.e. T-cell based), while others point to a crucial role of components of the innate immunity (i.e. some macrophage populations); again, there is evidence for both (and both are not mutually exclusive, of course). However, having stated these – admittedly – somewhat provocative hypotheses, it has also to be said that although animal models have failed thus far to provide the ultimate clue to the pathogenesis of psoriasis, much of our current notion of psoriasis actually stems from those models, and animal models have driven several lines of research in the human disease. Even if no animal model resembles the complete pathogenic network of human psoriasis, we have gained insight into the relevance of many cell types and/or molecules in the pathophysiology of chronic skin inflammation, aspects that presumably are relevant in the setting of psoriasis.

Overall, animal models have undoubtedly shed light on important functions of cells and mediators contributing to chronic cutaneous inflammation, but the uniform psoriasiform reaction pattern in many of these animals, regardless of the underlying molecular manipulation, appears to limit their suitability as true models of human psoriasis.

Why is it so difficult to interpret animal models of psoriasis?

Homogeneity of experimental animals versus heterogeneity of human patients

First, targeted mutations of single genes in mammals (mice in most cases) are usually introduced in animals of a homogeneous genetic background. In addition, most of these animals are kept under controlled conditions (e.g. specific pathogen-free conditions). These features alone are quite different from the situation in humans, where the clinical spectrum of psoriasis is rather broad (60,61) and where the disease is thought to result from interactions of several genetic susceptibility loci (6). Animal models only begin to reflect these aspects (39).

Imponderable influence of modifying genes

That modifying genes may influence the accrual of a psoriasiform phenotype is exemplified by several models, including spontaneous mutations [e.g. the flaky skin mutation that results in phenotypes of different severity depending on the genetic background; (20)] and genetically engineered animals [e.g. the CD18 hypomorphic mice ($Itgb2^{tm1Bay}/Itgb2^{tm1Bay}$), which show the psoriasis-like phenotype only when crossed into the PL/J strain; (39)]. In many cases, the potential influence of modifying genes in animal models is not sufficiently appreciated and needs further investigations.

Phenotype penetrance

The expression levels of the transgenes may greatly and unpredictably influence the phenotype in some animal models, as exemplified by IL-1α transgenic mice, which showed a more severe phenotype in animals with higher expression levels of the transgene (25) or BMP-6-transgenic animals, which showed a phenotype unlike psoriasis (i.e. epidermal atrophy) in a strain with high expression of the transgene (30). It is, therefore, conceivable that genetically engineered animals described as having no or weak hyperproliferative inflammatory phenotypes, such as IL-6 (23) or KGF (24) transgenic mice, could develop inflammatory changes if the transgenes were expressed at different levels (i.e. exceeding a quantitative threshold to initiate the inflammatory cascade), if the genetic background was altered, or if environmental factors (trigger factors) were changed.

Influence of environmental factors

That environmental factors influence the accrual and penetrance of psoriasis-like phenotypes is exemplified by a model based on adoptive transfer of minor histocompatibility mismatched $CD4^+/CD45RB^{hi}$ T cells into $Prkdc^{scid}$ mice, where penetrance and severity of the psoriasiform phenotype differed between different animal facilities and could be modulated by food and bedding of the animals (42,48,49).

Inherent differences between human and mouse skin

There are several considerable anatomical and physiological differences between human and mouse skin, which may profoundly impact on the phenotype of any disorder claimed to resemble psoriasis. Such inherent differences include, to name but a few, the thickness and architecture of the epidermis (2–3 layers in mice as compared with >6 in humans), the presence or absence of epidermal rete ridges, the density and length of hair follicles, the antigen expression pattern in follicular versus interfollicular epidermis, the constitutive presence of certain types of immune cells (e.g. dendritic epidermal T cells or $CD8^+$ dendritic cells), the epidermal turnover time, the thickness of the dermis or the presence of a panniculus carnosus in mice, but not in humans [reviewed in (8)].

'Psoriasis sells'

Sometimes, the prominent publication of a phenotype in laboratory animals may be facilitated if there is a connection to a specific human disease. It is, therefore, possible

that there is an inherent bias in the research community inasmuch as there may be a tendency to (over)-emphasise the similarity to psoriasis when chronic hyperproliferative inflammatory phenotypes are published. Indeed, without going into too much detail here, a glance at the last 25 primary publications of animal models (without the use of human material) exhibiting such a cutaneous phenotype shows that, papers stating the similarity to psoriasis upfront in the title have an average impact factor that is almost twice as high as compared with that of publications without the 'buzzword' psoriasis in the title. The phenotypes described in the respective papers, however, were sometimes not dramatically different. The reasons for that apparent tendency may be manyfold, and I will not speculate about them here. However, when interpreting chronic inflammation in animals, one may be well advised to check carefully which criteria may apply to study aspects of psoriasis and which ones do not.

Studying psoriasis in xenotransplantations of human skin

Given that animal models of psoriasis bear the abovementioned limitations, the currently best approach to study psoriasis in animals may be humanisation of mice, although the use of transplanted human skin may not be an animal model in the strict sense of the word. Humanisation of animals to study psoriasis comprises xenotransplantation of human skin and/or immune cells into immunodeficient animals (schematically depicted in Fig. 4) (62).

Nude mice lack functional T cells because of a mutated forkhead box transcription factor N1, resulting in defective thymus development (63). The humoral immune response is also impaired, possibly because of the absence of T helper cells. In contrast, the *Prkdc*^{scid} mutation causes a defect in the antigen receptor gene rearrangement of lymphocytes, resulting in a severe combined immune deficiency (SCID) of the T- and the B-cell system, that is in part reversible (leaky) (64,65). A similar phenotype without the handicap of potential leakiness results from deletion of *Rag-1* or *Rag-2* involved in the development of T and B cells (66,67).

Psoriatic skin retains its phenotype for more than 2 months following transplantation onto nude mice (68). Given that non-lesional skin grafted onto nude mice also adopted features of psoriatic skin (69), *Prkdc*^{scid}, *Rag*-deficient or AGR mice (AGR129 mice are mice deficient in type I (A) and type II (G) IFN receptors in addition to being *Rag-2*$^{-/-}$; either on a 129Sv/Ev or C57BL/6 background) were later used primarily as recipients in numerous studies [reviewed in (70)]. Depending on the purpose of the study, full-thickness or split-skin can be transplanted from clinically affected or non-affected human skin (71,72). The functional role of immune cells, T cells from the same individual in particular, has been extensively studied in such *Prkdc*^{scid}-hu transplantation models (73,74). Interestingly, this protocol triggered the development of psoriasis in the formerly unaffected skin from psoriasis patients, but not healthy donors (Fig. 4). In addition, the *Prkdc*^{scid}-hu model has helped to understand the role of bacterial superantigens as potential triggers for psoriasis (73). Molecules involved in epidermal recruitment of T cells, such as the $\alpha_1\beta_1$ integrin (75), and the contribution of resident T cells to the pathogenic cascade (76) have also been elucidated recently using xenotransplantation models.

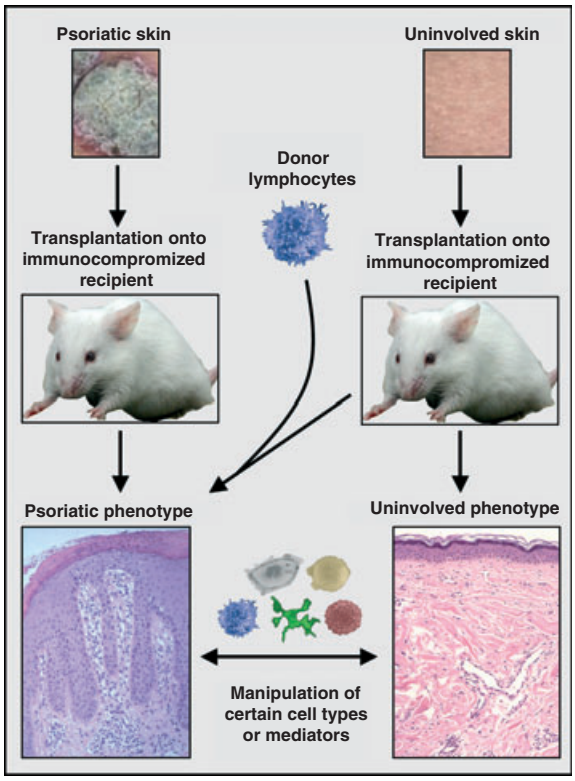

Figure 4. Xenotransplantation of human skin onto immunocompromised recipient mice. Grafts from lesional or non-lesional skin of psoriatic patients preserve their respective phenotypes following transplantation onto immunocompromised mice (e.g. *Prkdc*^{scid} mice, nude mice, AGR mice). Non-lesional skin, however, can be triggered to develop psoriatic features, e.g. by subsets of immune cells (lymphocytes, macrophages, dendritic cells). In addition, the functions of various cell types and/or molecules can be studied in xenotransplantation models.

In addition to components of the adaptive immune system, several publications using xenotransplantation of human skin onto mice substantiate a role of macrophages or other cells of the innate immune system for psoriasis-like skin alterations in mice. Infiltration of macrophages, especially in the vicinity of the dermo–epidermal junction,

is a typical feature of psoriasis (77). To interfere with innate immunity, reagents are available to deplete natural killer (NK) cells, neutrophilic granulocytes or macrophages. Alternatively, mice bearing the *Prkdc*^{scid} or the *Rag* mutations can be crossed into other strains affecting the innate immune system: non-obese diabetic (NOD) mice exhibit altered immune functions, including impairment of NK and antigen-presenting cells as well as the complement system (78). The beige mutation (*bg*^{J}/*bg*^{J}) affects NK cell function and granulocyte chemotaxis (79). Tolerance to xenografts is further enhanced in mice with several immune-relevant defects, such as NOD/*Prkdc*^{scid}, mice with additional targeted mutation of β2 microglobulin (NOD/*LtSz-scid/scid B2m*^{null}) (80) or a deletion of the common cytokine receptor γ-chain (81,82). Finally, there are so-called BNX mice bearing the beige (*bg*^{J}/*bg*^{J}), nude (*Foxn*^{nu}/*Foxn*^{nu}) and X-linked immunodeficiency mutation (*Btk*^{xid}/*Btk*^{xid}) (83).

For drug discovery and development, appropriate animal models should sufficiently mirror human psoriasis, be predictive, inexpensive, reproducible, easy to handle and should allow high throughput experiments. Unfortunately, none of the currently available models fulfils all of these criteria, necessitating the use of different models depending on the specific purpose. Humanised mouse models are important for studying targets, which are only expressed in human tissues, and for testing antibodies or biologics directed against human antigens (84).

What can we do and expect in the future?

Given that phenotypic characterisations are not truly comparable between the various animal models of psoriasis published thus far, it may appear questionable whether synopsis tables depicted in review papers (8,9) accurately reflect strengths and weaknesses of such models with respect to psoriasis features rather than summing up aspects arbitrarily analysed in the respective primary papers. In addition, penetrance and magnitude of phenotypes may critically depend on expression levels of transgenes (and/or copy numbers), environmental factors etc., as outlined above. Therefore, it is not at all precluded that (slight) modifications from the published conditions may impact significantly on the resulting phenotypes. Along this line, the influence of strain-dependent factors, i.e. modifying genes, has not been sufficiently explored yet. Thus, it may be worthwhile to compare animal models under consistent and uniform conditions, which need to be defined in a generally accepted fashion.

So, what can we hope for, short of truly full-fledged psoriasis in laboratory animals? First, I believe that we need to explore if and how different pathogenic aspects are interconnected in given models. This type of research has been tentatively initiated in some animal models, such as the CD18 hypomorphic mouse (*Itgb2*^{tm1Bay}/*Itgb2*^{tm1Bay} on the PL/J strain) in which elements of both adaptive (59) and innate immunity (56) have been investigated in the same model system and should now be brought together, possibly including additional aspects such as epidermal or vascular functions. Likewise, xenotransplantation models have been utilised to assess the role of resident cutaneous cells (85) as well as different immigrating cells and inflammatory mediators, indicating the individual relevance of a number of immune cell types (73–76), but failing thus far to sketch the 'big picture' of psoriasis. Expanding this line of research, it might be possible to dissect the relative contributions of parts of the immune system to the whole pathogenic mosaic. Hopefully, continuation of such studies and merging of individual aspects will ultimately pave the road to a more complete and unifying picture of the molecular and cellular network in the skin. Furthermore, I think that we need a more reliable means of comparison, preferably in a standardised manner, between human psoriasis and animal models on the one hand, and among the different animal models themselves on the contrary. Towards this end, we need to establish comparability criteria among different models as well as between animal models and human psoriasis. The first scoring system has recently been suggested (86) and now needs to be further developed and elaborated by the community of researchers in the field. Such an algorithm is predicted to be helpful to evaluate clinical, histopathological, immunological, biochemical, therapeutic and other parameters of the various models and to make them directly comparable.

Acknowledgements

The present work was supported by a Rudolf Virchow Award from the Deutsche Forschungsgemeinschaft and a research grant from the European Union (ANGIOSKIN, LSH-2003-512127) to MPS.

References

1 Griffiths C E, Barker J N. Pathogenesis and clinical features of psoriasis. Lancet 2007: **370**: 263–271.
2 Lowes M A, Bowcock A M, Krueger J G. Pathogenesis and therapy of psoriasis. Nature 2007: **445**: 866–873.
3 Sabat R, Philipp S, Höflich C *et al.* Immunopathogenesis of psoriasis. Exp Dermatol 2007: **16**: 779–798.
4 Schön M P, Boehncke W HPsoriasis. N Engl J Med 2005: **352**: 1899–1912.
5 Bos J D. Psoriasis, innate immunity, and gene pools. J Am Acad Dermatol 2007: **56**: 468–471.
6 Bowcock A M, Krueger J G. Getting under the skin: the immunogenetics of psoriasis. Nat Rev Immunol 2005: **5**: 699–711.
7 Valdimarsson H. The genetic basis of psoriasis. Clin Dermatol 2007: **25**: 563–567.

8 Gudjonsson J E, Johnston A, Dyson M, Valdimarsson H, Elder J T. Mouse models of psoriasis. J Invest Dermatol 2007: **127**: 1292–1308.

9 Schön M P. Animal models of psoriasis – what can we learn from them? J Invest Dermatol 1999: **112**: 405–410.

10 Dunstan R W, Rosser E R. Does a condition like human pityriasis rosea occur in pigs? Am J Dermatopathol 1986: **8**: 86–89.

11 Jayo M J, Zanolli M D, Jayo J M. Psoriatic plaques in *Macaca fascicularis*. Vet Pathol 1988: **25**: 282–285.

12 Lowe N J, Breeding J, Kean C, Cohn M L. Psoriasiform dermatitis in a rhesus monkey. J Invest Dermatol 1981: **76**: 141–142.

13 Mason K V, Halliwell R E, McDougal B J. Characterization of lichenoid-psoriasiform dermatosis in springer spaniels. J Am Vet Med Assoc 1996: **189**: 897–901.

14 Gates A H, Karasek M. Hereditary absence of sebaceous glands in the mouse. Science 1965: **148**: 1471–1473.

15 HogenEsch H, Gijbels M J J, Zurcher CThe chronic proliferative dermatitis (cpd) mutation, chromosome? In: Sundberg J Ped. Handbook of Mouse Mutations with Skin and Hair Abnormalities. Animal Models and Biomedical Tools. Boca Raton: CRC Press, 1994: 217–220.

16 Sundberg J P, France M, Boggess D *et al.* Development and progression of psoriasiform dermatitis and systemic lesions in the flaky skin (fsn) mouse mutant. Pathobiology 1997: **65**: 271–286.

17 Atochina O, Harn D. Prevention of psoriasis-like lesions development in fsn/fsn mice by helminth glycans. Exp Dermatol 2006: **15**: 461–468.

18 Beamer W G, Pelsue S C, Shultz L D, Sundberg J P, Barker J E. The flaky skin (fsn) mutation in mice: map location and description of the anemia. Blood 1995: **86**: 3220–3226.

19 Gijbels M J, Elliott G R, HogenEsch H, Zurcher C, van den HOven A, Bruijnzeel P L. Therapeutic interventions in mice with chronic proliferative dermatitis (cpdm/cpdm). Exp Dermatol 2000: **9**: 351–358.

20 Sundberg J P, Boggess D, Shultz L D, Beamer W GThe flaky skin (fsn) mutation, chromosome? In: Sundberg J Ded. Handbook of Mouse Mutations with Skin and Hair Abnormalities. Boca Raton: CRC Press, 1994: 253–268.

21 Sundberg J P, Dunstan R W, Roop D R, Beamer W G. Full-thickness grafts from flaky skin mice to nude mice: maintenance of the psoriasiform phenotype. J Invest Dermatol 1994: **102**: 781–788.

22 Vassar R, Fuchs E. Transgenic mice provide new insights into the role of TGFa during epidermal development and differentiation. Genes Dev 1991: **5**: 714–727.

23 Turksen K, Kupper T, Degenstein L, Williams I, Fuchs E. Interleukin 6: insights to its function by overexpression in transgenic mice. Proc Natl Acad Sci USA 1992: **89**: 5068–5072.

24 Guo L, Yu Q C, Fuchs E. Targeting expression of keratinocyte growth factor to keratinocytes elicits striking changes in epithelial differentiation in transgenic mice. EMBO J 1993: **12**: 973–986.

25 Groves R W, Mizutani H, Kieffer J D, Kupper T SInflammatory skin disease in transgenic mice that express high levels of interleukin 1a in basal epidermis. Proc Natl Acad Sci USA 1995: **92**: 11874–11878.

26 Li A G, Wang D, Feng X H, Wang X J. Latent TGFbeta1 overexpression in keratinocytes results in a severe psoriasis-like skin disorder. EMBO J 2004: **23**: 1770–1781.

27 Detmar M, Brown L F, Schön M P *et al.* Increased microvascular density and enhanced leukocyte rolling and adhesion in the skin of VEGF transgenic mice. J Invest Dermatol 1998: **111**: 1–6.

28 Xia Y P, Li B, Hylton D, Detmar M, Yancopoulos G D, Rudge J S. Transgenic delivery of VEGF to mouse skin leads to an inflammatory phenotype resembling human psoriasis. Blood 2003: **102**: 161–168.

29 Carroll J M, Crompton T, Seery J P, Watt F M. Transgenic mice expressing IFN-γ in the epidermis have eczema, hair hypopigmentation, and hair loss. J Invest Dermatol 1997: **108**: 412–422.

30 Blessing M, Schirmacher P, Kaiser S. Overexpression of bone morphogenic protein-6 (BMP-6) in the epidermis of transgenic mice: Inhibition or stimulation of proliferation depending on the pattern of transgene expression and formation of psoriatic lesions. J Cell Biol 1996: **135**: 227–239.

31 Voskas D, Jones N, van Slyke P *et al.* A cyclosporine-sensitive psoriasis-like disease produced in Tie2 transgenic mice. Am J Pathol 2005: **166**: 843–855.

32 Cook P W, Piepkorn M, Clegg C H *et al.* Transgenic expression of the human amphiregulin gene induces a psoriasis-like phenotype. J Clin Invest 1997: **100**: 2286–2294.

33 Kopp T, Kieffer J D, Rot A, Strommer S, Stingl G, Kupper T S. Inflammatory skin disease in K14/p40 transgenic mice: evidence for interleukin-12-like activities of p40. J Invest Dermatol 2001: **117**: 618–626.

34 Kopp T, Lenz P, Bello-Fernandez C, Kastelein R A, Kupper T S, Stingl G. IL-23 production by cosecretion of endogenous p19 and transgenic p40 in keratin 14/p40 transgenic mice: evidence for enhanced cutaneous immunity. J Immunol 2003: **170**: 5438–5444.

35 Blumberg H, Conklin D, Xu W F *et al.* Interleukin 20: discovery, receptor identification, and role in epidermal function. Cell 2001: **104**: 9–19.

36 D'Armiento J, DiColandrea T, Dalal S S *et al.* Collagenase expression in transgenic mouse skin causes hyperkeratosis and acanthosis and increases susceptibility to tumorigenesis. Mol Cell Biol 1995: **15**: 5732–5739.

37 Hobbs R M, Silva-Vargas V, Groves R, Watt F M. Expression of activated MEK1 in differentiating epidermal cells is sufficient to generate hyperproliferative and inflammatory skin lesions. J Invest Dermatol 2004: **123**: 503–515.

38 Carroll J M, Romero M R, Watt F M. Suprabasal integrin expression in the epidermis of transgenic mice results in developmental defects and a phenotype resembling psoriasis. Cell 1995: **83**: 957–968.

39 Bullard D C, Scharffetter-Kochanek K, McArthur M J *et al.* A polygenic mouse model of psoriasiform skin disease in CD18-deficient mice. Proc Natl Acad Sci USA 1996: **93**: 2116–2121.

40 Shepherd J, Little M C, Nicklin M J. Psoriasis-like cutaneous inflammation in mice lacking interleukin-1 receptor antagonist. J Invest Dermatol 2004: **122**: 665–669.

41 Hida S, Ogasawara K, Sato K *et al.* CD8(+) T cell-mediated skin disease in mice lacking IRF-2, the transcriptional attenuator of interferon-alpha/beta signaling. Immunity 2000: **13**: 643–655.

42 Schön M P, Schön M, Warren H B, Donohue J P, Parker C M. Cutaneous inflammatory disorder in integrin alphaE (CD103)-deficient mice. J Immunol 2000: **165**: 6583–6589.

43 Pasparakis M, Courtois G, Hafner M *et al.* TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK-2. Nature 2002: **417**: 861–866.

44 Sano S, Chan K S, Carbajal S *et al.* Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. Nat Med 2005: **11**: 43–49.

45 Zenz R, Eferl R, Kenner L *et al.* Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. Nature 2005: **437**: 369–375.

46 Hammer R E, Maika S D, Richardson J A, Tang J P, Taurog J D. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human b2m: an animal model of HLA-B27-associated human disorders. Cell 1990: **63**: 1099–1112.

47 Breban M, Fernandez-Sueiro J L, Richardson J A *et al.* T cells, but not thymic exposure to HLA-B27, are required for the inflammatory

disease of HLA-B27 transgenic rats. J Immunol 1996: **156**: 794–803.
48 Hong K, Chu A, Ludviksson B R, Berg E L, Ehrhardt R O. IL-12, independently of IFNgamma, plays a crucial role in the pathogenesis of a murine psoriasis-like skin disorder. J Immunol 1999: **162**: 7480–7491.
49 Schön M P, Detmar M, Parker C M. Murine psoriasis-like disorder induced by naive CD4+ T-cells. Nat Med 1997: **3**: 183–188.
50 Leon F, Contractor N, Fuss I *et al.* Antibodies to complement receptor 3 treat established inflammation in murine models of colitis and a novel model of psoriasiform dermatitis. J Immunol 2006: **177**: 6974–6982.
51 Nickoloff B J. Keratinocytes regain momentum as instigators of cutaneous inflammation. Trends Mol Med 2006: **12**: 102–106.
52 Stratis A, Pasparakis M, Rupec R A *et al.* Pathogenic role for skin macrophages in a mouse model of keratinocyte-induced psoriasis-like skin inflammation. J Clin Invest 2006: **116**: 2094–2104.
53 Nickoloff B J, Xin H, Nestle F O, Qin J Z. The cytokine and chemokine network in psoriasis. Clin Dermatol 2007: **25**: 568–573.
54 Nickoloff B J. Skin innate immune system in psoriasis: friend or foe? J Clin Invest 1999: **104**: 1161–1164.
55 Mössner R, Schön M P, Reich KTumor necrosis factor antagonists in the therapy of psoriasis. Clin Dermatol 2008: in press: doi: 10.1016/j.clindermatol.2007.1010.1030.
56 Wang H, Peters T, Kess D *et al.* Activated macrophages are essential in a murine model for T cell-mediated chronic psoriasiform skin inflammation. J Clin Invest 2006: **116**: 2105–2114.
57 Clark R A, Kupper T SMisbehaving macrophages in the pathogenesis of psoriasis. J Clin Invest 2006: **116**: 2084–2087.
58 Schön M, Denzer D, Kubitza R, Ruzicka T, Schön M P. Critical role of neutrophils for the generation of psoriasiform skin lesions in Flaky Skin mice. J Invest Dermatol 2000: **114**: 976–983.
59 Kess D, Peters T, Zamek J *et al.* CD4+ T cell-associated pathophysiology critically depends on CD18 gene dose effects in a murine model of psoriasis. J Immunol 2003: **171**: 5697–5706.
60 Murphy M, Kerr P, Grant-Kels J M. The histopathologic spectrum of psoriasis. Clin Dermatol 2007: **25**: 524–528.
61 Naldi L, Gambini D. The clinical spectrum of psoriasis. Clin Dermatol 2007: **25**: 510–518.
62 Igney F H, Asadullah K, Zollner T M. Humanised mouse models in drug discovery for skin inflammation. Expert Opin Drug Discov 2006: **1**: 53–68.
63 Flanagan S P. 'Nude,' a new hairless gene with pleiotropic effects in the mouse. Genet Res 1966: **8**: 295–309.
64 Bosma G C, Custer R P, Bosma M J. A severe combined immunodeficiency in the mouse. Nature 1983: **301**: 527–530.
65 Bosma M J, Carroll A M. The SCID mouse mutant: definition, characterization, and potential uses. Ann Rev Immunol 1991: **9**: 323–350.
66 Mombaerts P, Iacomini J, Johnson R S, Herrup K, Tonegawa S, Papaioannou V E. RAG-1-deficient mice have no mature B and T lymphocytes. Cell 1992: **68**: 869–877.
67 Shinkai Y, Rathbun G, Lam K P *et al.* RAG-2 deficient mice lack mature lymphocytes owing to inability to initiate V(D)J arrangement. Cell 1992: **68**: 855–867.
68 Krueger G G, Manning D D, Malouf J, Ogden B. Long-term maintenance of psoriatic human skin on congenically athymic (nude) mice. J Invest Dermatol 1975: **64**: 307–312.
69 Fraki J E, Briggaman R A, Lazarus G S. Uninvolved skin from psoriatic patients develop signs of involved skin after being grafted onto nude mice. Science 1982: **215**: 685–686.
70 Boehncke W H. The SCID-hu xenogeneic transplantation model: complex but telling. Arch Dermatol Res 1999: **291**: 367–373.
71 Boehncke W H, Sterry W, Hainzl A, Scheffold W, Kaufmann R. Psoriasiform architecture of murine epidermis overlying human psoriatic dermis transplanted onto scid mice. Arch Dermatol Res 1994: **286**: 325–330.
72 Nickoloff B J, Kunkel S L, Burdick M, Strieter R M. Severe combined immunodeficiency mouse and human psoriatic skin chimeras. Validation of a new animal model. Am J Pathol 1995: **146**: 580–588.
73 Boehncke W -H, Dressel D, Zollner T M, Kaufmann R. Pulling the trigger on psoriasis (letter). Nature 1996: **379**: 777.
74 Wrone-Smith T, Nickoloff B JDermal injection of immunocytes induces psoriasis. J Clin Invest 1996: **98**: 1878–1887.
75 Conrad C, Boyman O, Tonel G *et al.* Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nat Med 2007: **13**: 836–842.
76 Boyman O, Hefti H P, Conrad C, Nickoloff B J, Suter M, Nestle F O. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumour necrosis factor alpha. J Exp Med 2004: **199**: 731–736.
77 Boehncke W -H, Wortmann S, Kaufmann R, Mielke V, Sterry W. A subset of macrophages located along the basement membrane ('lining cells') is a characteristic histopathological feature of psoriasis. Am J Dermatopath 1995: **17**: 139–144.
78 Makino S, Kunimoto K, Muraoka Y, Mizushima Y, Katagiri K, Tochino Y. Breeding of a non-obese, diabetic strain of mice. Jikken Dobutsu 1980: **29**: 1–13.
79 Roder J, Duwe A. The beige mutation in the mouse selectively impairs natural killer cell function. Nature 1979: **278**: 451–453.
80 Christianson S W, Greiner D L, Hesselton R A *et al.* Enhanced human CD4+ T cell engraftment in beta2-microglobulin-deficient NOD-scid mice. J Immunol 1997: **158**: 3578–3586.
81 Ishikawa F, Yasukawa M, Lyons B L *et al.* Development of functional human blood and immune systems in NOD/SCID/IL2 receptor gamma chain null mice. Blood 2005: **106**: 1565–1573.
82 Shultz L D, Lyons B L, Burzenski L M *et al.* Human lymphoid and myeloid cell development in NOD/LtSz-scid IL2R gamma null mice engrafted with mobilized human hemopoietic stem cells. J Immunol 2005: **174**: 6477–6489.
83 Kamel-Reid S, Dick J E. Engraftment of immune-deficient mice with human hematopoietic stem cells. Science 1988: **242**: 1706–1709.
84 Boehncke W H. The psoriasis SCID mouse model: a tool for drug discovery? Ernst Schering Res. Found Workshop 2005: **50**: 213–234.
85 Boehncke W H, Schön M P. Animal models of psoriasis. Clin Dermatol 2007: **25**: 596–605.
86 Nickoloff B J. Psoriatic animal model validation index. J Invest Dermatol 2006: **126**: 59 (abstract).

