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Animal models of skin disease for drug discovery

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Abstract

Introduction—Discovery of novel drugs, treatments, and testing of consumer products in the field of dermatology is a multi-billion dollar business. Due to the distressing nature of many dermatological diseases, and the enormous consumer demand for products to reverse the effects of skin photodamage, aging, and hair loss, this is a very active field.

Areas covered—In this paper, we will cover the use of animal models that have been reported to recapitulate to a greater or lesser extent the features of human dermatological disease. There has been a remarkable increase in the number and variety of transgenic mouse models in recent years, and the basic strategy for constructing them is outlined.

Expert opinion—Inflammatory and autoimmune skin diseases are all represented by a range of mouse models both transgenic and normal. Skin cancer is mainly studied in mice and fish. Wound healing is studied in a wider range of animal species, and skin infections such as acne and leprosy also have been studied in animal models. Moving to the more consumer-oriented area of dermatology, there are models for studying the harmful effect of sunlight on the skin, and testing of sunscreens, and several different animal models of hair loss or alopecia.

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Declaration of interest

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Keywords

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1. Introduction

The use of animal models for drug discovery has increased at an exponential rate in recent years. The use of animal models of skin diseases is no exception to this general observation. Perhaps the single most important factor driving this enormous expansion of effort is the widespread development of transgenic mice. In fact, the variety and number of transgenic mouse models that have been reported in the area of dermatology alone has made compiling this review a daunting undertaking. Not only are transgenic mice widely employed, but also a bewildering variety of other animal models have been employed to mimic human skin conditions and diseases.

This review will cover the creation of transgenic mouse models and strategies for targeted gene disruption. Skin diseases and conditions for which animal models have been reported are then discussed under eight broad headings: inflammatory, blistering, autoimmune, cancer, wound healing, infection, photodamage, and alopecia.

1.1 Skin and hair in human and in animal models

Skin covers an area of 1.5 – 2.0 m² and accounts for almost 15% of the body weight (Figure 1) [1]. It provides resistance against trauma, provides protection against infections, prevents body from losing excess water, helps regulate the body temperature, synthesizes Vitamin D, and permits sensations of touch, heat, and cold [1].

It is composed of three layers: epidermis, dermis, and subcutaneous tissue. The epidermis, the outermost layer, is formed by keratinocytes, whose basic function is to synthesize keratin, a filamentous protein that has a protective function [2]. The dermis is the middle layer and its main component is the fibrillar structural protein collagen [2]. The dermis is situated on the top of subcutaneous tissue, which is composed of lobules of lipocytes [2].

Human and animal skins vary in many aspects; for example, percutaneous absorption of certain topical drugs is different among rabbits, rats, and pigs [3]. Amount of free fatty acids and triglycerides and the density of hair follicles seem to be important factors in the differences between the skin barriers of animals and human [4]. Rhesus monkey was found to be similar to human in terms of percutaneous absorption studies of hydrocortisone, testosterone, and benzoic acid [5]. Pig skin is also similar to human skin in its histological and biochemical properties, such as thickness, having follicular structures that extend deeply into the dermis, well-developed rete ridges and dermal papillary bodies, epidermal turnover time, abundant subdermal adipose tissue, vascular anatomy and collagen structure, and arrangement in the dermis [6,7]. However, adnexal differences exist between pig and human skin. For example, pig skin contains no eccrine glands, and unlike humans, apocrine glands are distributed through the skin surface [7]. Even though mice are commonly used as skin disease models, there are inherent differences in skin structure between mice and human skin. Mouse skin is significantly thinner, and global nucleotide excision repair (NER), the most important DNA repair mechanism acting in humans, appears less relevant in mouse skin [8]. In human skin, melanocytes are located in the basal layer of the epidermis, where they make dendritic connections with the surrounding keratinocytes [9,10]. Melanosomes are transferred from melanocyte to keratinocytes, providing skin pigmentation and also protection from ultraviolet radiation (UVR) [9]. However, in mouse skin, melanocytes are

located mainly at the base of the hair follicles embedded in the dermis and are only found in the epidermis of the hairless areas, that is ears, tail, and paws [9] or at dermal – epidermal junction at specific periods (e.g., during embryogenesis or postnatal) [11]. Discrepancies exist in both innate and adaptive immunity, including balance of leukocyte subsets, defensins, Toll receptors, inducible NO synthase, cytokines and cytokine receptors, Th1/Th2 differentiation, Ag-presenting function of endothelial cells, and chemokine and chemokine receptor expression [12]. Moreover, there are also differences in the cell signaling and functional profiles of oncogenes and tumor suppressor genes between mice and humans [13].

Differences exist between human and animal hair. For example, first two cycles of the mouse hair follicle are synchronized, whereas in humans, at a time when biopsies could be taken, surrounding follicles cycle independently from each other [14]. Mouse hair cycle is short, taking about 3 weeks, whereas human scalp hairs have a cycle time of several years [14]. This short synchronized hair cycle allows hair follicles to be harvested and examined at specific time points in the cycle very easily [14].

These differences should be taken into consideration while choosing a suitable animal model. We will try to mention important differences that may affect preference of one model to the other more in detail in each section.

1.2 Genetically engineered mouse animal models

Transgenic animals are used to study human disease, gene therapy, therapeutic substances, animal cloning, organ transplant, and so on. Transgenic animals are made by cloning the transgene of interest, and then inserting that gene into the genome of a newly fertilized egg. The egg is then cultured to the blastocyst stage and implanted into the uterus of a surrogate mother (Figure 2).

Several methods are administrated for delivering gene of interest to the target. These methods are classified as physical (microinjection), mechanical (e.g., gene gun, electroporation, laser irradiation), chemical (calcium phosphate precipitation, diethylaminoethanol (DEAE)-dextran), and biological (lipids, virus, plasmids), and currently, transgenic animals can be constructed in several ways such as microinjection [15], embryonic stem cell (ESC) injection [16], retroviral infection of pre or pro-implantation embryos [17], somatic cell nuclear transfer [18], and genetically modified sperm [19].

Various techniques are in use for creating genetically engineered animals such as mouse, rat, ship, pig, rabbit, fish, and drosophila. These techniques can be grouped as transgenes, targeted mutations (knockout and knock-in), random gene inactivation, and random gene mutations [20]. Targeted mutations are accomplished through homologous recombination (process by which a mutation is targeted to a precise location in the genome) in ESCs, followed by injection of modified ESCs into blastocytes and implantation into oviducts of foster females [20]. In the case of knockout models, targeted gene(s) is inactivated and the phenotype is due to the absence of the targeted gene product [21]. Knockout models of human genetic diseases have proven that a single gene defect is capable of causing disease [21]. In addition, the crossing of mice that are heterozygous or homozygous for specific gene mutations has provided significant information about skin diseases that are caused by multiple genetic defects [21]. It also enables the analysis of the function of a protein produced from a specific gene *in vivo* [21]. In case of knock-in model, targeted gene(s) are modified through targeted point mutation, addition, or deletion, instead of complete disruption of target gene expression, and the phenotype is due to the expression of modified gene product [20]. Random gene inactivation methods are accomplished when a gene-trap vector randomly inserts into a gene locus and interrupts transcription at the site of

integration [20]. Random mutagenesis, on the other hand, is done through generation of random point mutations across the genome, through controlled exposure to mutagenic chemicals or radiation [20]. Following this exposure, their progeny are screened for phenotypes, and multiple randomly mutated genes need to be mapped [20]. Hypomorphic approach is another method in designing a knockout mice, rather than using the classical method of knocking down the target genes. This approach facilitates the selection genetic function of interest to be expressed without compromising cell viability [22]. It has been used as a mouse model for generalized non-Herlitz junctional epidermolysis bullosa (JEB) [23] and generalized non-Herlitz JEB to find out the response to fibroblast therapy [24].

The first transgenic animal was a mice generated through the microinjection of viral gene transfer (simian virus 40 leukemia genes) to explanted mouse blastocysts [25] and early embryonic exposure to retroviruses [26]. Later on in 1982, Ralph Brinster in collaboration with Richard Palmiter inserted the structural gene for human growth hormone into mouse embryos, and noticed that the mice with the foreign gene grew much larger in size than those without the gene and also passed this trait to its offspring (Figure 2) [27].

Microinjection (Figure 2) exposes the fertilized egg to the transgene before the embryo forms, thus allowing the gene to be present in the embryo before development [28]. To do this, a fine-point glass pipette is used to microinject the DNA into a pronuclear stage embryo and integration occurs randomly as tandem arranged copies. Following this process, pronuclear stage embryos are transferred into the uterus of pseudopregnant recipient animals [28]. One main problem with microinjection is that, when DNA is introduced into the fertilized egg, DNA randomly inserts into the genome, and this might cause a disruption of the animal's normal gene functions. One method to overcome this drawback is by using certain viruses, such as adeno-associated virus which targets specific locations for transgene insertion that does not damage the host cell function. A second method is by using retroviruses which are more efficient in integrating foreign DNA, even though the integration site for retroviruses is most often random [29].

The method using ESCs (Figure 2) is somewhat similar to the microinjection technique, but involves making ESCs rather than fertilized eggs transgenic by injecting them with foreign DNA. During this process, in order to target a specific gene in epicutaneous sensitization (ES), a targeting construct is introduced into ESC by electroporation. This targeting construct is produced through a technique in which the second exon of the gene of interest is replaced by a neomycin resistance cassette, and a thymidine kinase (TK) cassette is included for negative selection. Finally, ESCs are injected back into another blastocyst which is implanted into a surrogate mother [30].

A different technique was developed to exert control over the pattern of expression of genetic changes introduced into the animal. This approach utilizes somatic cell recombination rather than germ cell (or ESC) recombination to inactivate a gene in restricted populations of cells or tissues. In this approach, a tissue-specific promoter is used to direct expression of one of the site-specific recombinases to limit gene inactivation to only those cells expressing the recombinase [31].

The recombinase system used for genetic manipulation in mice is the *Cre-lox* system from bacteriophage P1. The site-specific recombinase Cre (cyclization of recombination) is a 38-kDa protein from bacteriophage P1, which recognizes and catalyzes reciprocal DNA recombination between two *loxPn* (locus of crossing over of P1) sites. The *loxP* site is the 34-base pair (bp) recognition sequence for Cre composed of a palindromic 13-bp sequence separated by a unique 8-bp core sequence [30]. A loop is formed when four Cre proteins bind to two *loxP* sites (Figure 3). When the two *loxP* sites involved in the reaction are in the

same orientation, the recombination results in the excision of the DNA region flanked by the two *loxP* sites [32].

Conditional gene targeting relies on the insertion of *loxP* sites around a specific gene into the mouse genome by homologous recombination, a procedure that is now known as “floxing.” Mice bearing a “floxed” gene are then bred with mice expressing a Cre transgene controlled by a tissue-specific promoter (Figure 3). Some of the resulting progeny will harbor both the floxed region and express the Cre recombinase in specific cell types [20,32]. Various lines of Cre transgenic mice have been produced and additional lines are currently being characterized, thus continuously extending the cells or tissues where a gene of interest can be conditionally inactivated. This Cre-lox approach allows knockout of a gene only in a certain tissue to be done, where knockout of the gene in the whole mouse would be embryonic lethal.

Activation of expression of gene of interest in specific cell type at a specific point in time is made using inducible transgenic mouse models. Controlled gene expression in mouse models is studied based on the tamoxifen-inducible Cre recombinase system [33,34], Cre-loxP and the tetracycline (Tet)-inducible systems [35], and tet-operon/repressor bi-transgenic system, the estrogen receptor (ER) ligand-binding domain, the cell-specific activation and inactivation of gene expression are done using Tet-regulated [36] and Cre-ER systems which are complementary in mouse models like p16INK^{4+/-} [37,38]. The ER is most commonly fused with Cre recombinase, even though it can also be used with transcription factors such as kinases, which are active in the nucleus. Cre recombinase is most often found in combination with conditional alleles to inactivate gene expression, and when used for gene activation, Cre removes stop cassettes from transgenes and thus allows the expression of reporter or other molecules. Thus, the Tet-regulated and Cre-ER systems are complementary in animal models, through utility in the cell-specific activation and inactivation of gene expression [37].

Another approach is to insert a transgene for a toxin receptor or for a foreign enzyme under the control of a promoter specific to a certain cell type. An example of the former is the diphtheria toxin receptor [39], and an example of the later is viral TK that can produce a lethal toxin from gancyclovir [40]. If, for instance, either of these genes were expressed only in dendritic cells (DCs), the administration of diphtheria toxin or gancyclovir to the mice would temporarily deplete the mouse of DCs for a period depending on the dosing regimen.

2. Inflammatory disease

2.1 Atopic dermatitis

Atopic dermatitis (AD) is a chronic, relapsing inflammatory cutaneous disease (Figure 4). Two major models currently exist to recapitulate the pathogenesis of AD. The first model describes AD as a result of impaired epidermal barrier function due to intrinsic structural and functional abnormalities in the skin where the disease evolves from the outside, with an abnormal epidermal barrier as the primary defect [41]. The second model views AD as primarily an immune function disorder in which Langerhans cells, T-cells, and immune effector cells modulate an inflammatory response to environmental factors [42]. Unlike the common belief that was widely accepted for a very long time, there is now little support for the view that AD is the result of allergies [43,44]. Immune responses to allergens, irritants, and microbes that enter the skin through a defective skin barrier may contribute to the development of local inflammatory responses and the cutaneous findings of AD. Antigen-presenting cells in the skin, in particular immunoglobulin E (IgE)-bearing Langerhans cells, may be interacting with these environmental allergens, leading to the local Th2-mediated inflammatory responses that have been detected in the skin of patients with AD [45].

Patients with mild-to-moderate AD typically have much lower (or normal) serum IgE levels when compared to patients with severe AD, which suggests that the systemic Th2-driven axis of the immune system detected in AD might be related to epidermal barrier dysfunction and the introduction of environmental antigens, rather than intrinsic immune hypersensitivity [46,47]. Various models have been developed and each model is suitable for research of different stages and types of AD.

These models can be categorized into three groups: i) models induced by allergen; ii) genetically engineered transgenic mice that either overexpress or lack selective molecules; iii) mice that spontaneously develop AD-like skin lesions. These models display many features of human AD, and their study has resulted in a better understanding of the pathogenesis of this disease.

2.2 AD model induced by allergen

2.2.1 Passive sensitization model—This model shows IgE-mediated cutaneous inflammation reaction which is carried out by intravenous injection of murine monoclonal IgE anti-hapten antibodies [48]. Within several minutes after injection, cutaneous inflammatory reactions become evident. It can be used to study the early-phase allergic reaction mediated by IgE-sensitized mast cells. The status can last for 24 – 48 h, which can be used to investigate the antigen-specific triggering of sensitized T cells.

2.2.2 Epicutaneous sensitization model—Repeated ES is induced by tape-stripped skin with allergen including ovalbumin (OVA), house dust mite, and haptens. Tape-stripped skin imitates skin barrier dysfunction and it can respond to allergen more easily [49]. ES-sensitized mice manifest increased scratching behavior with developing epidermal hyperplasia. The skin pathological manifestation shows CD4⁺ T cell and eosinophil infiltration, and upregulated expression of Th2 cytokines, including interleukin 4 (IL-4), IL-5, and IL-13 with little or without interferon-gamma (IFN- γ) expression [50]. OVA-sensitized mice developed airway hyperresponsiveness following inhalation challenge with OVA [50].

On the other hand, mice-sensitized features by the recombinant house dust mite allergen were similar to those observed with EC sensitization models with OVA, and manifested epidermal hyperplasia and spongiosis (intracellular swelling within the epidermis), infiltration of CD4⁺ and CD8⁺ cells, and a skewed Th2 response locally and systemically [51].

Using oxazolone and trinitrochlorobenzene as haptens can induce allergic contact dermatitis and evoke primarily a Th1-dominated response. However, it has been reported that multiple challenges with haptens of the skin over an extended period cause the skin inflammation to shift from Th1-dominated responses to chronic Th2-dominated inflammatory responses that are similar to those in human AD patients [52]. Furthermore, repeated challenge with oxazolone has reported to induce a chronic Th2-like skin inflammation, presented the clinical feature with epidermal hyperplasia, and suppresses expression of the skin differentiation proteins including filaggrin, loricrin, and involucrin [52]. It can mimic the dysfunction barrier of AD.

Superantigenic properties of *Staphylococcus aureus* are the most common cause of AD exacerbates. Application of SEB instead of OVA by repeated EC sensitization to tape-stripped skin was able to elicit Th2-dominated allergic skin inflammation accompanied by a systemic Th2 response to the superantigen [53].

Food allergen is also a type of pathogenic factor in a subset of AD patients [54]. Repeated intragastric sensitization of C3H/HeJ mice with cow's milk or peanut, with cholera toxin as adjuvant, caused hair loss, scratching, and chronic relapsing AD-like skin lesions in up to 35% mice, accompanied by elevated serum levels of specific IgE and blood eosinophilia [55].

2.3 Genetically engineered mouse models of AD

2.3.1 Flaky tail mice—The genotype of flaky tail (FLG^{ft}) mice cannot express functional filaggrin from the cornified layer in the epidermis which does not form normal keratohyalin F granules and is not proteolytically processed to filaggrin. These mice exhibited eczematous skin lesions mimicking human AD after age 28 weeks under specific pathogen-free conditions and a progressive increase in serum IgE and IgG 1 levels. Eight-week-old flaky tail mice demonstrated epidermal hyperplasia, enhanced dermal infiltration of CD4⁺ cells, and expression of mRNA for IL-17, IL-6, and IL-23, but not IL-4, IL-13, or IFN- γ . Lesional skin of 32-week-old filaggrin-deficient mice exhibited more pronounced changes and elevated IL-4 mRNA levels. These findings indicated that flaky tail mice demonstrate Th17-dominated skin inflammation and eczematous dermatitis with advancing age change [56].

2.3.2 Apolipoprotein C1 transgenic mice—Although human apolipoprotein C1 transgenic (APOC1Tg) mice were developed as a model for hyperlipidemia, they are a useful model for inflammatory dermatitis. APOC1Tg mice spontaneously develop age-severe dermatitis with moderate epidermal hyperplasia, hyperkeratosis and parakeratosis, scaling, lichenification, dermal infiltration of inflammatory cells, and pruritus [57]. They display a disturbed skin barrier and can be used to study the role of skin barrier integrity in the pathogenesis of AD.

2.3.3 NC/Tnd Mice—NC mice were established as an inbred strain from Japanese fancy mice by Kondo *et al.* [58]. NC/Tnd mice are inbred strains originating from NC/Nga and express spontaneous AD most precisely. Itchy dermatitis develops in NC/Tnd mice kept under conventional conditions without air regulation from 6 to 8 weeks of age. The skin lesions of NC/Tnd mice show epidermal hyperplasia, degranulation of mast cells, and recruitment of inflammatory cells. DCs are accumulated into the hyperplastic epithelia. In addition, IL-4 and Th2-specific chemokines are overproduced [59], indicating that Th2-type immune responses are upregulated as well as in human subjects with AD in the initial phase. The content of ceramide in the skin is remarkably decreased in NC/Tnd mice before dermatitis, and it became clear that trans-epidermal water loss was promoted in the affected skin as a result [60].

2.3.4 IL-4 transgenic mice—Transgenic mice overexpressing IL-4 in the skin develop spontaneous pruritus and chronic dermatitis at the age of 4 months [61]. It can be used to study the different stages of AD with features similar to human AD.

2.3.5 RelB knockout mice—RelB^{-/-} mice exhibit spontaneous dermatitis, hyperkeratosis, acanthosis, skin infiltration with CD4⁺ T cells and eosinophils, and elevated serum IgE, all features of human AD [62], although pruritus was not reported.

2.3.6 SC chymotryptic enzyme transgenic mice—Overexpression of a human SC chymotryptic enzyme transgene in suprabasal epidermal keratinocytes of mice led to the development of AD-like skin starting at the age of 7 – 8 weeks or older [63].

2.3.7 IL-31 transgenic mice—IL-31 transgenic mice overexpressing IL-31, driven by the lymphocyte-specific promoter Lck or by the ubiquitous elongation factor-1a promoter, exhibited signs of dermatitis at the age of 2 months, including pruritus, mild-to-moderate hair loss, and considerable thickening of ear skin. Histological examination of skin lesions revealed hyperkeratosis, acanthosis, inflammatory cell infiltration and an increase in mast cells, which resemble the skin lesions of human AD. However, these mice exhibited normal serum concentrations of IgE [50]. The evaluation of local or systemic T_H2 response was not reported.

2.3.8 NOA (Naruto Research Institute Otsuka Atrichia) mice—The phenotype of NOA mice is characterized by ulcerative skin lesions with the accumulation of mast cells, elevated serum IgE, and scratching behavior. Accumulation of mast cells and elevated serum IgE may be a model for elements of AD.

2.3.9 TSLP transgenic mice—TSLP transgenic mice overexpressing TSLP and skin erythema occurred at over 2 – 3 weeks of doxycycline treatment, and progressed to AD-like changes, including persistent erythema, mild xerosis, crusting, and erosions at 3 – 4 weeks. Histological examination of skin lesions showed changes similar to those observed in human AD, and exhibited a T_H2 cell profile with the upregulation of IL-4, IL-5, and tumor necrosis factor-alpha (TNF-α). These mice also showed elevated serum levels of IgE and IgG1 and decreased IgG2a [64].

2.3.10 Caspase-1 and IL-18 transgenic mice—Transgenic mice overexpressing the human caspase-1 (CASP1) precursor gene in epidermal keratinocytes showed elevated serum levels of IgE and IgG1 at the age of 8 weeks and mild pruritic dermatitis around the eyes and ears at the age of 16 weeks [65]. Histological examination showed prominent acanthosis, papillomatosis, parakeratosis, and intracellular edema with dense infiltration of lymphocytes, neutrophils, and mast cells, but not eosinophils in the skin lesion. The mouse model may mimic intrinsic AD. IL-1β-deficient CASP1 and IL-18 transgenic mice exhibited similar dermatitis [66].

2.3.11 Cathepsin E knockout mice—Cat E^{-/-} mice on C57BL/6 background developed pruritic and erosive skin lesions, from which *S. aureus* was identified [67]. These mice could be a good model for studying the role of APCs in AD pathogenesis.

2.4 Spontaneous mouse models of AD

Nc/Nga mice are an inbred mouse strain, the first mouse model of AD reported [58]. Skin changes develop spontaneously in Nc/Nga mice secondary to the exposure to various environmental aeroallergens and closely mimic human AD. AD-like disease only develops when mice are kept under conventional conditions rather than barrier housing. Histological examination shows dermal infiltration with eosinophils and mononuclear cells before the appearance of clinical skin manifestations. Hyperparakeratosis, hyperplasia, and spongiosis were observed in the skin lesions.

Other strains of mice that spontaneously develop dermatitis have been proposed as alternative models of AD. DS-Ng mice, another inbred strain, have been reported to develop spontaneous dermatitis only under conventional conditions. Moreover, heavy colonization of *S. aureus* was found in skin lesions. Therefore, these mice could be a good model for *S. aureus*-associated AD [68].

3. Psoriasis

Psoriasis is an inflammatory skin disease with no permanent cure. Psoriatic skin contains increased number of immune cells that produce high numbers of cytokines, chemokines, and inflammatory molecules (Figure 5) [69]. The epidermis divides at a much faster rate than normal and has a defective outer layer which under normal circumstances protects from infection and dehydration (Figure 5) [69]. Animal models are very popular for the study of psoriasis. Krueger's group tested an antibody directed against IL-15 that was known to inhibit the production of T lymphocytes as well as the liberation of TNF- α *in vitro* [70]. Application of this antibody in severe combined immunodeficient mice (SCID) led to the disappearance of psoriatic characteristics.

Spontaneous mutation mouse models, such as homozygous asebia (Scd1ab/Scd1ab) mutant mice [71], Flaky skin mice (Ttcfns/Ttcfns) [72], spontaneous chronic proliferative dermatitis mutation mice [73] and so on, do not closely mimic the disease enough to be considered as good models of psoriasis. They must rather be used to compare local pathogenic events such as hyperkeratosis, regulation of neutrophil infiltration and micro-abscess formation, or dermal angiogenesis [71]. Nearly a hundred mouse mutations that lead to psoriasiform phenotypes have been documented.

Genetically engineered mice represent the largest category of psoriasis models. These include the transgenic and knockout models, such as human leukocyte antigen B27 (HLA-B27) transgenic rats [74], CD18 hypomorphic mice [75], K14/VEGF and Tie2 mice [76,77], K14/TGF- α , K5/TGF- β 1, K14/KGF and K14/IL-20 transgenic mice [78–80], IKK2 [81] and JunB/c-Jun transgenic mice [82], K5.Stat3C mice [83], and K14/IL-6 and K14/IL-1 α transgenic mice [84]. Hansson *et al.* [63]. developed a transgenic mouse strain that overexpresses the chymotryptic enzyme, which is also overexpressed in the stratum corneum of psoriatic skin. Pathological characteristics of psoriasis can be observed in this model.

4. Blistering skin disorders

4.1 Pemphigus

Pemphigus is an acute or chronic, bullous autoimmune disease of skin and/or mucous membranes [85]. Loss of normal cell-to-cell adhesion occurs as a result of circulating IgG antibodies binding and attacking to desmoglein (Dsg) which is a transmembrane glycoprotein found in desmosomes that is a member of cadherin superfamily [85]. Pemphigus can be classified as Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF). While Anti-Dsg 1 antibodies in PF cause acantholysis in superficial epidermis of the skin, in deep dermis Dsg 3 compensates loss of function of Dsg 1 [85]. In early PV, antibodies are present only against Dsg 3 without compensatory Dsg 1 and therefore it presents with blisters only in the deep mucous membrane [85]. However, in mucocutaneous pemphigus, antibodies against Desmoglein 1 (Dsg1) and Dsg3 are both present and blisters are found in the skin as well as in mucous membranes [85].

Null mutation Desmoglein 3 mice display severe erosions of the oral mucosa (similar to that seen in PV patients) that prevented them from feeding. Overt skin lesions were not noted in these mice, except for areas exposed to significant mechanical stress such as the skin around the snout, the nipples of nursing females, and the mucocutaneous junctions in the eyes [86,87]. A histological examination of other mouse-stratified epithelium tissues that express Dsg3, such as the esophagus, the forestomach, and the thymus, did not reveal abnormalities. Note that the forestomach is a characteristic feature of the mouse which is not present in humans [88].

Null mutation Desmocollin 3 (Dsc3) in mice mimics the effect of loss of Dsg3, and these mice can develop spontaneous skin blisters, leading to PV-like histopathology [88]. Lesions in the Dsc3 null mice were found to be restricted to the skin and were absent in internal stratified epithelia, such as those of the oral cavity.

4.2 Epidermolysis bullosa

EB covers a spectrum of rare genodermatoses in which a disturbed coherence of the epidermis and/or the dermis causes blister formation following trauma [85]. It is classified according to the site of blister formation, and the main three groups are epidermolytic or EB simplex (EBS), JEB, and dermolytic or dystrophic EB (DEB) [85]. Transgenic mice have been developed as models for different forms of EB [89]. Examples include the transforming growth factor- β -induced, myofibroblast-mediated contractile fibrosis in severe DEB [90] and the Langerhans cell-mediated inflammatory processes described in keratin 5-deficient mice [91]. Of particular interest was the suitability of EB mouse models for preclinical testing of gene-, protein-, and cell-based therapies [92,93]. The collagen VII knockout mouse has been used for pilot studies of protein replacement- and cell-based treatments [93], but the short life span of the mouse has prevented long-term follow-up and limited the interpretation of results [94–96]. The recently developed type VII collagen hypomorphic mouse and mice with milder phenotypes [90], which have a longer life span, may be better suited for preclinical testing, and they have already proven useful.

4.3 Bullous Pemphigoid

Bullous Pemphigoid (BP) is the most common serious autoimmune blistering skin disease, which presents with pruritic papular and/or urticarial lesions with large tense bullae. Autoantibody interacts with bullous pemphigoid antigen [BPAG1 and BPAG2 (collagen type XVII)] in hemidesmosomes of basal keratinocytes and this is followed by complement activation and attraction of neutrophils and eosinophils.

Interestingly, passive transfer of human autoantibodies from patients with BP into mice does not induce skin lesions, and most likely explanation is that humans and mice in the amino acid sequence of the collagen type XVII pathogenic epitope might be different [97]. To overcome this challenge, a novel molecular method has been established which is through ‘humanization of autoantigen’ by genetic manipulation [98]. By using collagen type XVII-humanized mouse, two different mouse models have been established; one is by injecting human autoantibodies from BP patients into the neonatal collagen type XVII-humanized mice and the other model was induced by mouse antibodies to human collagen type XVII passively transferred from mother via placenta and milk into the neonatal collagen type XVII-humanized mice [98]. Both models provide the opportunity to study pathophysiology and treatment options for this debilitating disease.

5. Autoimmune diseases

5.1 Introduction to autoimmune diseases

Although significant progress has been made in management of autoimmune diseases over the last decade, unfortunately cures for these diseases have not yet been found [99]. One of the challenges faced in drug discovery is the fact that most autoimmune diseases have extremely heterogeneous clinical presentations, and animal models cannot completely replicate the real biological complexity underlying the human disease [99]. Additionally, just like in other models, various differences exist between the human and rodent immune systems, and since immune dysfunctions are at the root of autoimmune diseases, such differences cause limitations when extrapolating from animal models to autoimmune patients [99]. Recent discoveries have shown that genetic susceptibility to autoimmune

diseases involves a large number of genes with small individual contributions, but in spite of this great complexity, significant advances have been made and a small but growing number of susceptibility genes have been identified [99]. Experimental models of autoimmune diseases can be divided into several broad groups: i) inbred mice which spontaneously develops a systemic lupus erythematosus (SLE)-like disease; ii) chronic graft vs host diseases (GvHDs) induced in F1 hybrid mice injected with lymphoid parental cells; iii) UV light-irradiated mice immunized with some DNA components; iv) immune-deficient mice such as SCID mice and nude mice inoculated or engrafted with immunocompetent cells or tissues, and v) gene-manipulated mice such as transgenic or knockout mice [100].

5.2 Systemic lupus erythematosus

LE commonly presents in women of young age and ranges from limited and exclusive skin involvement in chronic tissues LE to life-threatening manifestations of acute SLE [85]. Overall, 85% of patients with LE have skin lesions [85]. SLE, which is a more serious and multisystemic form, is based on polyclonal B-cell immunity and involves connective tissue and blood vessels. Fever, skin lesions, arthritis, and central nervous system, renal, cardiac, and pulmonary diseases are common. On skin, it presents with a butterfly rash on the cheeks [85]. Anti-double-stranded DNA, anti-Sm antibodies, and rRNP antibodies are specific for SLE [85].

Even though most of the mouse models mentioned above have been used for SLE [101], the most common group is inbred strains. The main examples of SLE-prone mice are New Zealand Black (NZB), F1 hybrids of NZB $\times$ New Zealand White (NZW) (B/W F1), MRL/Mp-lpr/lpr, and BXSB mice (Table 1) [100–102]. The MRL/lpr mouse is a good model for spontaneous development of skin lesions similar to those seen in SLE, and is frequently used in cutaneous lupus studies [100]. In this model, lpr mutation causes an alteration in the *Fas* gene and a defect of apoptosis, which in turn result in abnormal lymphocyte proliferation with abnormal function and autoantibody production [103]. Characteristic skin lesions seen in these mice are dermal inflammatory infiltrates which consist of T cells and immunoglobulin and/or complement component deposition at the dermal – epidermal junction [100,103]. Over the last decade, the most important finding in terms of models of SLE was the discovery of Fas defect in pathogenesis of autoimmune MRL/lpr mouse, which is a good model for spontaneous development of skin lesions similar to those seen in human LE [104]. Transgenic and knockout mice provided further opportunity to investigate cutaneous LE [104]. Model of drug-induced cutaneous LE provides additional insight since the trigger is already known in drug-induced LE [104]. An alternative way to induce cutaneous lesions is through TCR alpha $-/-$ mice that are treated with fluorouracil and UVB light irradiation [104]. Macroscopically, the MRL/lpr mouse also shows alopecia lesions with erythematous changes, and histological changes in the epidermis, vasodilation, and bleeding are all observed [100]. The NZB/KN mouse is another model that shows alopecia lesions but this time with neither scab formation nor erythematous changes and immunohistologically subepidermal IgM deposits are often demonstrated. Therefore, these two models seem to be useful for murine autoimmune alopecia (Table 1) [100]. Arteritis, often a result of infection or autoimmune response, is defined as inflammation of the walls of arteries.

5.3 Scleroderma

Scleroderma (aka systemic sclerosis or SSc) is commonly a multisystem disorder characterized by inflammatory vascular and sclerotic changes of the skin and various internal organs, specifically the lung, heart, and gastrointestinal tract [85]. Calcinosis cutis, raynaud phenomenon, esophageal dysfunction, and telangiectasia are common features of

SSc [85]. Detection of anticentromeric antibodies and DNA topoisomerase I (Scl-70) antibodies aids the diagnosis [85].

Animal models of SSc can be divided into three groups (Table 2) [105,106]. The first group contains naturally occurring disease models in which mutations that have occurred during the breeding process have been maintained (e.g., Type 1 tight skin mouse – Tsk1/+, UCD-200 chickens). In these models, SSc-like features develop spontaneously. The second group comprises induced models which are elicited by chemical exposure or cell transplantation [e.g., bleomycin-induced SSc in skin and lung, and transplantation of mismatched immune cells to give sclerodermatous GvHD]. The third group contains models that are created by genetic manipulation through mutagenesis or defined genetic modification such as gene knockouts or differential expression of genes. Although all the animal models display fibrotic skin changes resembling those in SSc patients, a model which shows all the pathogenetic components together with histologic and biochemical features of human SSc is not yet available (Table 2).

5.4 Dermatomyositis

Dermatomyositis (DM) is a systemic disease that is a subtype of idiopathic inflammatory myopathies and is characterized by heliotrope (inflammatory changes and/or edema of the eyelids and periorbital area), erythema of the face, neck, and upper trunk, flat-topped purplish papules over the knuckles, polyomyositis, interstitial pneumonitis, and myocardial involvement [85]. Calcification in subcutaneous fascial tissues is common later in course of juvenile DM [85]. Autoantibodies to 155 kDa Se are present in 80% of the patients; however, specificity is low. In addition to this, autoantibodies to antinuclear antibodies (nuclear and speckled pattern) are also present in 40% of the cases [85].

Two kinds of species are used as animal models for DM, i.e., rats and dogs. Juvenile DM is seen in Collies and Shetland sheepdogs (Shelties) and is characterized by a cicatricial alopecia and hypopigmentation of the face, limbs, and extremities, preceded by erythema, papules, and vesicles [107]. Histologically, lymphocytes, mast cells, and macrophages are seen distributed throughout the dermis [107]. Some affected animals present with a concurrent myositis [108]. When rats were sensitized with a vitamin-D derivative, dihydrotachysterol, and subsequently challenged by ferric dextran plus certain histamine liberators such as polymyxin, musculocutaneous inflammation, which resembles DM, was observed [109]. Erythema, edema, pain in skin of face, ears, and frontal extremities, and stomatitis presented in the second and third day, which was followed between third and sixth days by induration with non-pitting edema of skin, scales, and muscular weakness [109].

6. Skin cancer

Since drug discovery efforts are frequently directed against cancer, animal models have been developed against the three principle types of skin cancer: squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma.

6.1 Squamous cell carcinoma

SCC is mainly studied in mice. Transgenic expression of ErbB2, Src, Fyn, and MEK-1 kinases driven by keratin promoters in epidermis spontaneously produce cutaneous SCC [13]. On the other hand, K14-ER:Ras transgenic mice, which harbor a tamoxifen-inducible Hras G12V, present a Ras-dependent epidermal hyperplasia which is associated with impaired differentiation that resembles SCC *in situ* [13]. Transgenic mouse lines with increased STAT3 (family of transcription factors that regulate various target genes involved in apoptosis, angiogenesis, and cell cycle regulation) also demonstrate spontaneous and UVB-induced cSCC [13]. Injection of nude mice with Notch1-deficient primary

keratinocytes expressing activated Ras treated with a Notch signaling inhibitor results in the formation of poorly differentiated and invasive SCC [13].

6.2 Melanoma

A variety of rodent and non-rodent melanoma models have been studied for melanoma research. Swine (Duroc-Jersey swine, Sinclair miniature swine, Munich Troll miniature swine) [110] and Camargue horses develop melanoma; however, neither of these develop melanoma with a sunlight-based etiology [10]. Melanomas have been reported in Syrian hamster and several guinea pigs; however, tumors were induced by exposure to 7,12-dimethylbenzanthracene which is a chemical carcinogen with unknown etiological relevance, and in these models melanoma was not induced by UV alone [10]. Models that are responsive to UVR are the marsupial *Monodelphis domestica*, genetic hybrids between platyfish and swordtails, and different species of the fresh water fish genus *Xiphophorus* [10,111]. Transgenic models are also in use both in mouse [112] [e.g., HGF/SF (hepatocyte growth factor/scatter factor transgenic mouse) [10], Cdk4R24C transgenic mice [9]] and fish (e.g., zebrafish – *Danio rerio* and in medaka – *Oryzias latipes*) [111]. Zebrafish is one of the most powerful animal models for melanoma and contributes to various aspects of drug development processes, including target identification, disease modeling, lead discovery, and toxicology. Each female is capable of laying 200 – 300 eggs per week, external fertilization allows manipulation of embryos *ex utero*, and rapid development of optically clear embryos allows the direct observation of developing internal organs and tissues *in vivo* [113]. Zebrafish melanocytes are externally visible and single cells which can be visualized in a living fish [114]. While in human, melanin pigment-containing melanosomes are transported to neighboring keratinocytes, zebrafish melanocytes retain melanin and this serves as a reliable cell-type marker [114]. Furthermore, the development of melanocytes from the embryonic neural crest is well characterized [114]. It provides a unique opportunity for transgenic models, both forward and reverse genetic analysis, and to uncover insights into the molecular genetics of cancer [113]. Forward and reverse genetic strategies are used to present significant advantages for the discovery of tumor suppressor genes which induce tumorigenesis when activated [113]. High-throughput modifier screens which are based on zebrafish cancer models lead to identification of chemicals or genes involved in the suppression or prevention of the malignant phenotype, and identifying these small molecules or gene products through such screens aids novel drug development for the treatment of melanoma and other cancer types [113].

6.3 Basal cell carcinoma

Targeted inactivation of the Shh, Ptch, Smo, and Gli genes, which are all involved in sonic hedgehog signaling (SHH) pathway, has enabled important insights into BCC development, proliferation, and oncogenesis [115]. Overexpression of SHH in the skin of transgenic mice demonstrated skeletal and skin anomalies with the development of BCC-like tumors reminiscent of the NBCC syndrome [115]. In addition, regenerated human skin transgenic for SHH, grafted onto immune-deficient mice, revealed abnormal BCC-like structures. BCC-like tumors also develop in mice overexpressing Gli1 and Gli2 which are downstream modulators of SHH [115]. While in heterozygote transgenic PTCH mice, BCC lesions are not found, when these mice are chronically exposed to UV, they develop microscopic BCC lesions, 40% of which present with p53 mutations [115]. Similar microscopic BCC-like lesions have been observed in transgenic mice carrying a constitutively active mutated SMO gene as well [115]. However, tissue growth environment is another important issue to consider, since BCC from SHH transgenic mice transplanted onto the backs of SCID mice, did not differentiate, stopped growing, and did not metastasize, which indicates that their own specific stroma is required for BCC development [115].

7. Wound models

7.1 Cutaneous wound healing

Cutaneous wound healing is a complex multifaceted biological process that involves multiple tissue types influenced by local as well as systemic factors (Figure 6) [116,117]. A successful experimental model will encapsulate each phase to better understand the mechanistic features of wound repair and the development of biological therapeutics for clinical use [118]. A wide variety of models have been developed that examine different aspects of the skin repair response. An *in vivo* model utilizing animal subjects has the advantages of simulating wound repair that is most similar to clinical cases. For example, the host's vascular and immune systems, as well as the external environment, influence animal models like humans [119]. In this section we have described the most widely used *in vivo* models in skin tissue repair research.

7.2 Excisional wound model

Full-thickness dermal wound results in damage to many structures, cell layers, and lineages, and different processes can be evaluated, viz. epithelialization, contraction, dermal reconstitution, inflammation, chemotaxis, angiogenesis, matrix production/organization, and cosmetic and functional outcome. The healing efficacy of different novel types of dressings, dermal substitutes, and local and external therapeutic agent can be investigated by this model [120]. Many of the species used for this type of investigation (mouse, rat, guinea pig, rabbit, and hamster) have a subcutaneous panniculus carnosus muscle, which contributes to the repair via contraction and collagen formation. However, this structure is absent in humans. Anatomically and physiologically, pig skin is more similar to human skin and it has been found that porcine model is an excellent tool for the evaluation of therapeutic agents destined for use in human wounds. In contrast, hairless mouse ear wound model heals entirely by re-epithelialization and granulation tissue formation without contraction. Rabbit ear wound model has been used as an ischemic model as well as for investigating hypergranulation [118].

7.3 Superficial wound models

This type of model is mainly used in experiments related to skin. Several techniques are used to separate different layers of the skin (dermatome, sucking, tape stripping, etc.). Blister wound model is produced by suction using different types of devices producing standardized, small epidermal blebs. The model can be used both in animals and in humans for evaluation of epidermal regeneration and the influence of different compounds and drugs [121]. Partial-thickness excision wound model is produced by a hand-held or electrical dermatome. The model can be used for evaluation of local environmental factors and topical agents. Donor sites are widely used as one of these models in humans [122].

7.4 Head and splinted wound models

Splinted wounds, where an overlying frame is attached to the wound edge, and skin wounds on the head, where there is no underlying musculature, both cause a retardation of wound contraction. A very high proportion of the splinted wounds in the diabetic mouse model (approximately 80%) showed a retardation of contraction [123]. The healing of splinted wounds of diabetic mice mimics closely the wound healing in human patients, with the main processes being re-epithelialization and granulation tissue formation. Laser photobiomodulation that stimulated healing in splinted wounds in diabetic mice has been reported [123].

7.5 Embryonic wound models

Unlike in adult skin, wound healing in early gestational stage mammalian embryos involves repair processes that result in the essentially perfect regeneration of damaged tissue [124]. The cellular and molecular differences between scar-free healing in embryonic wounds and scar-forming healing in adult wounds have recently been investigated and have led to the development of several animal models in which fetal scar-less healing has been described. These include the sheep, pig, rabbit, mouse, rat, guinea pig, chicken, opossum, and monkey [125]. The embryonic wounds that heal without a scar have lower numbers of less-differentiated inflammatory cells and low levels of TGF- β 1, TGF- β 2, platelet-derived growth factor (PDGF), and high levels of TGF- β 3. The recent studies have allowed the identification of therapeutic targets in the form of novel pharmaceutical molecules, which markedly improve or completely prevent scarring during adult wound healing in experimental animals [126,127].

7.6 External traumatic wound infection models

The external traumatic wound has been studied with experimental infections in animal models of surgical site wounds, burns, skin abrasions, lacerations, excisional wounds, and open fractures [128]. Studies were carried out which varied in the animal species used, microorganism strains, the number of microorganisms applied, the size of the wounds, and, for burn infections, the length of time the heated object or liquid is in contact with the skin [128]. An innovative technique has been developed employing bioluminescent (glow-in-the-dark) bacteria and low-light imaging cameras to noninvasively monitor the progress of the infection in real time in the same animal [129]. This technique dramatically reduces the number of animals needed in each experimental group to obtain statistical significance when testing antimicrobial drugs or preparations. Figure 7 illustrates the use of this approach in mouse models to monitor methicillin-resistant *S. aureus* infection in a partial-thickness skin abrasion [130] and *Acinetobacter baumannii* infection in a third-degree burn [131]. Among various antimicrobial strategies presently being investigated are targeted photodynamic therapy, silver preparations (nanocrystalline and slow release), antimicrobial peptides, skin substitutes, chitosan preparations, new iodine delivery formulations, phage therapy, and natural products such as honey and essential oils [130].

7.7 Chronic wound models

Impaired wound healing may be a consequence of pathologic states associated with malnutrition, ischemia, diabetes, venous stasis, pressure, or treatment with steroids, chemotherapy agents, or radiation, and in injuries such as burns, frostbite, and gunshots. Impaired wound healing is also a problem for immobilized patients and the elderly. On other hand, hypertrophic and keloid scarring are characterized by hyperproliferation of wound fibroblasts and overproduction of extracellular matrix proteins. Multiple pathogenic abnormalities have roles in impaired healing, including phenotypic changes in resident wound cells, excessive exudate, and altered matrix metalloproteinases profiles, and the presence of biofilms and bacterial colonization. Models that parallel these problems have been developed [132].

Abnormalities associated with diabetic wounds include prolonged inflammation, impaired neovascularization, decreased synthesis of collagen, increased levels of proteases, defective macrophage function, and infection. The murine models for type 1 diabetes range from animals with spontaneously developing autoimmune diabetes (non-obese diabetic mice) to chemical ablation of the pancreatic beta cells (streptozotocin, alloxan) and genetically and virally induced diabetes. Type 2 diabetes is modeled in both obese and non-obese animal models with varying degrees of insulin resistance and beta cell failure. In addition, models of beta cell regeneration and the use of knockout and transgenic models in diabetic wound

research are also considered by many researchers [133]. The wound-healing deficiency in these models suggests that the etiology for the wound healing impairment is due to the diabetic state, and to the hypo- or hyperinsulinemia, nor the respective defects of each model, i.e., the leptin receptor defect, the streptozotocin, or the immunologic defect of the NOD mouse [134]. Healing impairment in burns is characterized by increased free-radical-mediated damage, delayed granulation tissue formation, reduced angiogenesis, and decreased collagen reorganization; moreover, it is highly susceptible to infection leading to chronic wound healing. There have been many types of burn models used for examining wound healing and the systemic response to thermal injury [132]. Recently, efficacy of different novel pharmacotherapeutic agents and tissue-engineered wound dressings have been evaluated for augmenting nonhealing diabetic and burn wounds [118].

8. Skin infection models

8.1 Leprosy

Leprosy is a skin disease caused by *Mycobacterium leprae* and is still endemic in certain countries in the world. It is usually not recognized until a cutaneous eruption occurs, but 90% of patients present with numbness first, sometimes years before the skin lesions appear. Temperature sensitivity by the skin is lost in the initial stages of the disease, followed by vision loss and pain. These symptoms are especially apparent in the hands and feet. A hypopigmented macule is often the first cutaneous lesion. From this stage, most lesions evolve into the lepromatous, tuberculoid, or borderline types. The fact that leprosy affects predominantly the skin, nasal mucosa, and peripheral nerves suggested that the temperature at which *M. leprae* multiplies optimally is less than 37°C (Brand, 1959).

Even though *leprosy bacillus* was the first of the family of mycobacteria to be shown to cause disease in human, *M. leprae* still remains as the only known bacteria causing disease in man that has not been cultured *in vitro* [135]. It was only in 1960 that even an animal model became available, with the local and limited growth of *M. leprae* in the mouse following footpad inoculation. Footpad was the preferred site of inoculation since it is a cooler site (30°C), which mirrors the preferred cooler sites in human leprosy, permits serial sampling of the tissue as the infection progresses, and there is a minimum of inflammatory response in the footpad tissues [135,136]. In normal immunologically intact rodents the footpad infection is limited. *M. leprae*-infected mice are resistant to a second challenge. On the assumption that these limited infections were the result of a cell-mediated immune response, *M. leprae* infections were studied both for investigation and drug discovery in various immune-deficient and nude rodents in an attempt to obtain greater yields of *M. leprae*. In 1971, nine-banded armadillo animal model was introduced as an alternative model providing the opportunity for studying in detail the bacteriology, chemotherapy, immunology, and pathogenesis of leprosy [135]. Various characteristics like low body temperature (32 – 35°C), regular production of monozygotic quadruplet young, and a long life span (estimated to be 15 years) make nine-banded armadillo (*Dasypus novemcinctus* Linn) a favorable model for lepromatous leprosy [137].

8.2 Acne

Acne causes pimples including blackheads, whiteheads, and red inflammatory patches of skin. *Propionibacterium acnes* infection of the sebaceous glands is closely associated with acne, but additional etiologic factors may be involved. *P. acnes* are anaerobic Gram-positive bacteria and cause inflammation leading to scarring in severe cases. The list of animal models that have been used in the study of acne include the rabbit ear model, rhino mouse model [138], Mexican hairless dog model [138,139], Golden Hamster model, swine, and guinea pig [140].

8.3 Viral infections

Compared to bacterial infections, viral infections are more complex and difficult to model in animals. Herpes simplex is a viral infection, and transmission of the virus occurs when the genital or oral mucosa of the uninfected person comes in contact with virus shed by an actively infected person. Symptomatic cases may represent either primary infection with herpes simplex virus (HSV) or recurrent disease, since the herpes viruses have the ability to remain latent in the involved nerve root between outbreaks, and when activated cause recurrent infections. Recurrent infections due to loss of immune system might be severe and disseminated in immunocompromised patients. Even though most infections are caused by herpes simplex virus type 2 (HSV-2) and transmitted by sexual contact, some cases might be caused by HSV-1 as well. The infection primarily involves the epidermal layer in the skin with focal epidermal destruction, leukocytic infiltration of the epidermis and adjacent dermis, and cytological changes in infected epidermal cells typical for HSV. Commonly used animal models for herpes simplex are the albino guinea pig and the hairless guinea pig [141,142].

Varicella-zoster virus (VZV) infection is commonly seen as a benign disease of children causing fever and vesicular skin lesions [143]. However, in the adolescent or adult and in immune-compromised patients, it may be more severe. Complications include pneumonia, hepatitis, and encephalitis. VZV causes disease only in humans, and attempts to produce the disease by experimental infection of animals with VZV have led to seroconversion but not to disease itself [144]. However, clinical, pathological, immunological, and virological evidence suggests that simian varicella virus infection of non-human primates is the counterpart of human VZV infection [144]. For this reason, patas monkeys and the African green monkeys of either sex are being used as experimental models for VZV [144,145].

8.4 Leishmaniasis

Leishmaniasis is a disease complex caused by obligate intracellular, protozoan parasites of the genus *Leishmania*. Depending upon the species, infection can manifest itself in humans viscera, mucocutaneously, or cutaneously. Inbred mice strains are most commonly used for experimental cutaneous leishmaniasis (CL) infections. Different strains of mouse vary in their susceptibility to strains and species of *Leishmania* [146]. Furthermore, different parts of the mouse anatomy (such as base of tail, footpad, and ear) have different susceptibilities to cutaneous Leishmaniasis infection [147]. The Syrian or golden hamster (*Mesocricetus auratus*) is the recommended species of hamster for infections of *L. mexicana*, *L. panamensis*, and *L. braziliensis*, although other types of hamsters have been used as well [148].

9. Photodermatology

9.1 Photoaging

Photoaging is a term which was coined by Kligman and Kligman in 1986 to describe the various changes that develop after many years of cutaneous exposure to UVR [149]. Excessive exposure to solar UVR causes severe acute damages to the skin, which include erythema, sunburn, immunosuppressant, and also long-term effects such as photoaging and skin cancer [150–154]. The pathophysiological basis for human cutaneous photoaging is not well understood, but there are many companies focusing on its prevention and reversal by various consumer products. Aging is a complex process in which several mechanisms operate simultaneously. These include accumulation of mutations in the genome, accumulation of toxic metabolites, hormonal deprivation, increased formation of free radicals (oxidative damage), and cross-linking of macromolecules by glycation [155]. Although both photoaging and chronological aging are associated with wrinkles,

photoaging-induced wrinkles are regarded as deeper and more coarse, whereas those associated with chronological aging are generally more superficial and delicate [156].

C57BL/6J, SKH1, and BALB/c mice are the three main strains used for photoaging and photocarcinogenesis studies [157–159]. Meena R. Sharma *et al.* tested these three strains for a potential animal experimental model for acute photodamage studies. Adult females were exposed to UVB and then evaluated 3 or 20 h after the last irradiation. Results demonstrated that skin from UVB-exposed C57BL/6J mice showed features resembling human photodamage, namely epidermal thickening, infiltration of the dermis with inflammatory cells, induction of TNF- α mRNA, accumulation of glycosaminoglycans, particularly hyaluronan in the epidermis, and loss of collagen. Hairless SKH1 mouse skin responded similarly; however, there was no induction of TNF- α mRNA or chondroitin sulfate. Irradiated BALB/c mice, on the other hand, were least similar to humans in response to UVB irradiation.

Many researchers have attempted to demonstrate that the solar elastosis type of photodamage is accompanied by an increase in elastin and fibrillin messenger RNAs and elastin promoter activity [160]. A line of transgenic mice that expresses the human elastin promoter linked to a chloramphenicol acetyltransferase (CAT) reporter gene was used to demonstrate the effect of the long-term UV exposure, which can cause major alterations in the papillary dermis, which results in the deposition of massive amount of abnormal elastic material which is called solar elastosis [160]. This model is also useful in order to investigate the potential effects of sunscreen on photoaging and photodamage prevention since measured changes in solar elastosis also represent the amount of photodamage caused by UV.

Solar-induced damage to mitochondria in skin fibroblasts is proposed to be one of the key factors in premature photoaging of human skin, and the defective powerhouse model (mtDNA mutator mice) has been used in order to demonstrate this phenomenon [161].

9.2 Photocarcinogenesis

Photocarcinogenesis is the sum of complex simultaneous and sequential biochemical events that finally leads to the occurrence of skin cancer. These events are initiated by UVR of certain wavelengths, and include formation of DNA damage products, DNA repair, and mutation of proto-oncogenes and tumor suppressor genes [162]. Recently, in SKH-1 hairless mice the effects of NO-exisulind on the growth of UVB-induced skin tumor development have been investigated [163]. Jantschitsch *et al.* [159]. used female C57BL/6J mice lacking p35 (IL-12p35 $^{-/-}$) and p19 (IL-23p19 $^{-/-}$) which were subjected to chronic UVR exposure, and they found that lowering the load of DNA damage either by modulating the NER or by other mechanisms is an essential component of the sun protection strategies.

9.3 Photoprotection

To develop compounds that may protect against sun damage, mice and guinea pigs have mainly been used. Among mice models, the hairless mouse, especially the albino mouse, is preferred, since it has advantages over other mouse strains with its bare skin that is just like the human skin. Its lack of tanning ability due to its lack of pigments in the skin causes it to be highly susceptible to skin cancer and the sun protection factor (SPF) of a sunscreen can be measured directly [164]. The disadvantage of using mice as a model is that the thicknesses of mouse skin and human skin are not exactly the same, nor are the human and murine responses to solar-simulated radiation (SSR) [160]. Unlike guinea pigs, mice do not develop marked erythema and therefore edema development is used for evaluation [165]. This might be due to different substances released in mast cells of each species, while

guinea pig mast cells release histamine and mouse mast cell mainly releases serotonin, which is known to produce edema in the rodent [165]. Transgenic mice containing the human elastin promoter linked to a CAT reporter gene have been suggested as a model [160]. This transgenic mouse can be used to measure the response to single exposures of UV emitted from a fluorescent source, and since promoter induction is one of the primary events causing elastin production in skin, this model provides a precise measurement of one of the earliest events leading to photoaging [160]. It has also been used in measuring the protection from SSR afforded by sunscreens with increasing SPF [160]. The mouse ear model also shows good correlation with SPF as determined on human subjects [166]. In one study it was used as a mouse model of contact photoallergy to 3,3',4',5-tetrachlorosalicylanilide (TCSA) [167]. Mice were sensitized with TCSA painting plus UVA irradiation (TCSA/UVA) on the abdomen and, 5 days later, sun screen agents were applied to the earlobes and subsequently challenged with TCSA/UVA [167]. Their protective efficacy was evaluated in the degree of inhibition of both ear-swelling responses and TCSA–epidermal cell photoadduct formation [167].

The xeroderma pigmentosum (XPA) mice model, on the other hand, is XPA gene deficient and therefore is defective in NER and consequently shows high incidence of skin tumors and severe acute inflammation in response to UVB irradiation [168]. The guinea pig (Hartley strain) is a reliable test model for protection against UVA-induced erythema with a solar-simulated source and is convenient and relatively inexpensive for testing photoprotection agents [169,170].

10. Hair disorders

10.1 Alopecia areata

Alopecia areata (AA) like hair loss has been observed in several species, including monkeys, dogs, cats, horses, cattle, poultry, and non-human primates [171,172]. However, the use of these species in AA research is restricted due to their limited numbers, genetic variability, and scattered geographical distribution [172], and, therefore, inbred rodent strains are likely to be ideal research models. Several rodent models with spontaneous and induced AA have been identified, and of these, C3H/HeJ mice and Dundee experimental bald rat (DEBR) are the most commonly used models. The DEBR model develops spontaneous AA at a higher frequency than in the mouse model; however, the disadvantage of this model is that they are more expensive to use in drug studies owing to their larger size [173]. The low frequency of AA and not being able to predict the stage of AA as it evolves in the naturally occurring C3H/HeJ model of AA can be converted into a predictable system by grafting full-thickness skin from AA-affected mice to normal haired mice of the same strain [173]. Human scalp explants on SCID mice is another experimental model reported by Kyoizumi and colleagues [174] and later adapted by Gilhar and colleagues [175]. These workers transplanted samples of involved scalp tissue from AA patients into subcutaneous tissue of SCID mice and the graft tissue was then injected with autologous T lymphocytes which had been isolated from affected scalp [175]. The Smyth line chicken model is not yet widely used; however, it also shows promising results for future use, both in alopecia areata and alopecia universalis [176]. Table 3 shows a brief summary of commonly used mouse strains with histologically confirmed AA-like diseases [172].

10.2 Androgenetic alopecia

The stump-tailed macaque monkey model is currently the model of choice for human androgenetic alopecia even though it has certain disadvantages such as being expensive, dangerous, and difficult to obtain. At puberty, macaques exhibit frontal scalp baldness in both sexes, and its interplay of both genetic and hormonal factors which regulate follicular

regression is very similar to those seen in human androgenetic alopecia. In rodent models, on the other hand, both testosterone-induced alopecia and various xenograft approaches seem to be promising for development of new therapies to treat hair loss. Animal models of androgenetic alopecia are summarized in Table 4 [177,178].

10.3 Chemotherapy-induced alopecia

Chemotherapy-induced alopecia (CIA) is one of the most distressing side effects of cancer chemotherapy and little progress has been made due to lack of suitable experimental models. Mice, rats, and rabbits are the animal models that have been studied so far (Table 5) [178–182]. The main difference in hair growth on human vs rodent skin/scalp is the growth pattern, which can be either mosaic or wave pattern [182]. In wave pattern, the entry of hair follicles begins from the head and moves toward the tail, which is a pattern seen in neonatal rats and hair loss in CIA [182]. CIA occurs when hair follicles are in anagen phase and almost 90% of hair follicles in human scalp are in the anagen phase lasting 2 – 6 years, less than 1% are in the catagen phase lasting 2 – 3 weeks, and around 10% are in telogen phase lasting 3 – 4 months [182]. Animal models of CIA typically involve procedures that cause the hair follicles to enter the anagen growth phase in order to be able to mimic the human scenario [182]. Two main approaches are used: i) neonatal rats that show spontaneous anagen hair growth and ii) synchronizing the hair follicles in adult mice by depilation (Table 5) [178,182].

11. Expert opinion

An astonishing array of animal models has been reported in the field of skin disease. The explosion in the variety and availability of transgenic mice in recent years has led to the creation of models that were unheard of only a few years ago. The overall goal of the creators of these animal models is two-fold: first to gain insight into, and deeper understanding of, the pathogenesis, progression, and molecular biology of these cutaneous diseases; and secondly, to discover and test new drug therapies and also non-pharmacological approaches to treatment. Some examples of important drugs that have had important contributions made in their development by animal models are the following.

Drug discovery efforts in animal models for skin disease have been most notable in the psoriasis SCID mouse model where efalizumab (Raptiva®) [183] and infliximab (Remicade®) [184] were both discovered. Drug discovery for dermatitis has been less well developed, although there is a skin xenotransplantation model “Trans *in vivo* delayed hypersensitivity model” using an antigen-specific immune response that is relevant for both psoriasis and AD [185]. The antihuman CD4 Mab (HuMax-CD4) was developed in this model, by inhibiting proliferation of T-cells. The rhino mouse com-edolytic model and the hairless mouse photoaging model are established animal models for screening the *in vivo* activity of retinoids [186]. Vismodegib [187] is a potent and selective inhibitor of the Hedgehog (Hh) pathway that showed antitumor activity in patient-derived colorectal cancer xenograft tumor models and medulloblastoma allograft tumors driven by mutational or ligand-dependent activation of the Hh pathway. Interestingly, it was not tested in animal models of BCC, perhaps because good BCC models do not exist. Results published in the New England Journal of Medicine suggested that vismodegib might represent a new “gold-standard” treatment for patients with BCC that is extremely advanced, or which has begun to spread.

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Bibliography

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kenneth, S., editor. Human anatomy. International edition. McGraw Hill; Ohio: 2007.
2. William, D.; James, TGB.; Elston, Dirk M. Andrews' diseases of the skin. 10. Clinical Dermatology; Canada: 2000.
3. Bartek MJ, LaBudde JA, Maibach HI. Skin permeability in vivo: comparison in rat, rabbit, pig and man. *J Invest Dermatol*. 1972; 58(3):114–23. [PubMed: 4622425]
4. Netzlaff F, Schaefer UF, Lehr CM, et al. Comparison of bovine udder skin with human and porcine skin in percutaneous permeation experiments. *Altern Lab Anim*. 2006; 34(5):499–513. [PubMed: 17121474]
5. Wester RC, Maibach HI. Percutaneous absorption in the rhesus monkey compared to man. *Toxicol Appl Pharmacol*. 1975; 32(2):394–8. [PubMed: 1154403]
6. Godin B, Touitou E. Transdermal skin delivery: predictions for humans from in vivo, ex vivo and animal models. *Adv Drug Deliv Rev*. 2007; 59(11):1152–61. [PubMed: 17889400]
7. Sullivan TP, Eaglstein WH, Davis SC, et al. The pig as a model for human wound healing. *Wound Repair Regen*. 2001; 9(2):66–76. [PubMed: 11350644]
8. Garcia M, Llamas S, Garcia E, et al. In vivo assessment of acute UVB responses in normal and Xeroderma Pigmentosum (XP-C) skin-humanized mouse models. *Am J Physiol*. 2010; 177(2):865–72.
9. Zaidi MR, Day CP, Merlino G. From UVs to metastases: modeling melanoma initiation and progression in the mouse. *J Invest Dermatol*. 2008; 128(10):2381–91. [PubMed: 18787547]
- 10•. Ha L, Noonan FP, De Fabo EC, et al. Animal models of melanoma. *J Invest Dermatol Symp Proc*. 2005; 10:2–86. A review from the leading workers in the field of mouse and other animal models of melanoma.
11. Becker JC, Houben R, Schrama D, et al. Mouse models for melanoma: a personal perspective. *Exp Dermatol*. 2010; 19(2):157–64. [PubMed: 19849715]
- 12•. Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. *J Immunol*. 2004; 172:5–2731. A timely reminder of the differences that exist between mice and humans with particular relevance to the immune system.
13. Ratushny V, Gober MD, Hick R, et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. *J Clin Invest*. 2012; 122(2):464–72. [PubMed: 22293185]
14. Porter RM. Mouse models for human hair loss disorders. *J Anat*. 2003; 202(1):125–31. [PubMed: 12587927]
15. Capecchi MR. The new mouse genetics: altering the genome by gene targeting. *Trends Genet*. 1989; 5(3):70–6. [PubMed: 2660363]
16. Brosnan MJ, Chen LH, Wheeler CE, et al. Phosphocreatine protects ATP from a fructose load in transgenic mouse liver expressing creatine kinase. *Am J Physiol*. 1991; 260(6 Pt 1):C1191–200. [PubMed: 2058653]
17. Wight DC, Wagner TE. Transgenic mice: a decade of progress in technology and research. *Mutat Res*. 1994; 307(2):429–40. [PubMed: 7514717]
18. Strachan, T.; Read, AP. Human molecular genetics. 2010/12/07. Wiley-Liss Inc; New York: 1999.
19. Kurita K, Burgess SM, Sakai N. Transgenic zebrafish produced by retroviral infection of in vitro-cultured sperm. *Proc Natl Acad Sci USA*. 2004; 101(5):1263–7. [PubMed: 14745028]
- 20•. Chen J, Roop DR. Genetically engineered mouse models for skin research: taking the next step. *J Dermatol Sci*. 2008; 52:1–1. Useful review of transgenic mouse models for various skin diseases. [PubMed: 18511240]

21. Kupper TS. The utility of transgenic mouse models in the study of cutaneous immunology and inflammation. *J Dermatol.* 1996; 23(11):741–5. [PubMed: 8990695]
22. Baker DJ. Hypomorphic mice. *Methods Mol Biol.* 2011; 693:233–44. [PubMed: 21080283]
23. Bubier JA, Sproule TJ, Alley LM, et al. A mouse model of generalized non-Herlitz junctional epidermolysis bullosa. *J Invest Dermatol.* 2010; 130(7):1819–28. [PubMed: 20336083]
- 24••. Fritsch A, Loeckermann S, Kern JS, et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. *J Clin Invest.* 2008; 118:5–1669. Reports a novel hypomorphic mouse model of a human blistering disease and shows it can be used for testing a new therapeutic approach.
25. Jaenisch R, Mintz B. Simian virus 40 DNA sequences in DNA of healthy adult mice derived from preimplantation blastocysts injected with viral DNA. *Proc Natl Acad Sci USA.* 1974; 71(4):1250–4. [PubMed: 4364530]
26. Jaenisch R. Germ line integration and Mendelian transmission of the exogenous Moloney leukemia virus. *Proc Natl Acad Sci USA.* 1976; 73(4):1260–4. [PubMed: 1063407]
27. Palmiter RD, Brinster RL, Hammer RE, et al. Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. *Nature.* 1982; 300(5893):611–15. [PubMed: 6958982]
28. Boverhof DR, Chamberlain MP, Elcombe CR, et al. Transgenic animal models in toxicology: historical perspectives and future outlook. *Toxicol Sci.* 2011; 121(2):207–33. [PubMed: 21447610]
29. Vanderbilt JN, Allen L, Gonzalez RF, et al. Directed expression of transgenes to alveolar type I cells in the mouse. *Am J Respir Cell Mol Biol.* 2008; 39(3):253–62. [PubMed: 18367724]
30. Pinkert, CA. Transgenic animal technology - a laboratory handbook. 2. Academic Press; New York: 2002.
31. Heyer J, Kwong LN, Lowe SW, et al. Non-germline genetically engineered mouse models for translational cancer research. *Nat Rev Cancer.* 2010; 10(7):470–80. [PubMed: 20574449]
32. Gassmann M, Hennet T, Bauer C. Transgenic mice in basic research. *Schweiz Arch Tierheilkd.* 1998; 140(5):198–204. [PubMed: 9617206]
33. Leone DP, Genoud S, Atanasoski S, et al. Tamoxifen-inducible glia-specific Cre mice for somatic mutagenesis in oligodendrocytes and Schwann cells. *Mol Cell Neurosci.* 2003; 22(4):430–40. [PubMed: 12727441]
34. Metzger D, Chambon P. Site- and time-specific gene targeting in the mouse. *Methods.* 2001; 24(1):71–80. [PubMed: 11327805]
35. Heine HL, Leong HS, Rossi FM, et al. Strategies of conditional gene expression in myocardium: an overview. *Methods Mol Med.* 2005; 112:109–54. [PubMed: 16010014]
36. Sun Y, Chen X, Xiao D. Tetracycline-inducible expression systems: new strategies and practices in the transgenic mouse modeling. *Acta Biochim Biophys Sin (Shanghai).* 2007; 39(4):235–46. [PubMed: 17417678]
37. Saunders TL. Inducible transgenic mouse models. *Methods Mol Biol.* 2011; 693:103–15. [PubMed: 21080277]
38. Albanese C, Hulit J, Sakamaki T, et al. Recent advances in inducible expression in transgenic mice. *Semin Cell Dev Biol.* 2002; 13(2):129–41. [PubMed: 12240598]
39. Bennett CL, Clausen BE. DC ablation in mice: promises, pitfalls, and challenges. *Trends Immunol.* 2007; 28(12):525–31. [PubMed: 17964853]
40. Mailly L, Leboeuf C, Tiberghien P, et al. Genetically engineered T-cells expressing a ganciclovir-sensitive HSV-tk suicide gene for the prevention of GvHD. *Curr Opin Investig Drugs.* 2010; 11(5):559–70.
41. Elias PM, Steinhoff M. “Outside-to-inside” (and now back to “outside”) pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol.* 2008; 128(5):1067–70. [PubMed: 18408746]
42. Chan LS. Atopic dermatitis in 2008. *Curr Dir Autoimmun.* 2008; 10:76–118. [PubMed: 18460882]
43. Sandilands A, Smith FJ, Irvine AD, et al. Filaggrin’s fuller figure: a glimpse into the genetic architecture of atopic dermatitis. *J Invest Dermatol.* 2007; 127(6):1282–4. [PubMed: 17502856]

44. McGrath JA, Uitto J. The filaggrin story: novel insights into skin-barrier function and disease. *Trends Mol Med*. 2008; 14(1):20–7. [PubMed: 18068483]
45. Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol*. 2000; 105(5):860–76. [PubMed: 10808164]
46. Cork MJ, Robinson DA, Vasilopoulos Y, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol*. 2006; 118(1):3–21. quiz 22–3. [PubMed: 16815133]
47. Flohr C, Johansson SG, Wahlgren CF, et al. How atopic is atopic dermatitis? *J Allergy Clin Immunol*. 2004; 114(1):150–8. [PubMed: 15241359]
48. Maekawa S, Ovary Z. Correlation of murine anti-dinitrophenyl antibody content as determined by ELISA, passive cutaneous anaphylaxis and passive hemolysis. *J Immunol Methods*. 1984; 71(2): 229–39. [PubMed: 6376637]
49. Spergel JM, Mizoguchi E, Oettgen H, et al. Roles of TH1 and TH2 cytokines in a murine model of allergic dermatitis. *J Clin Invest*. 1999; 103(8):1103–11. [PubMed: 10207161]
50. Jin H, He R, Oyoshi M, et al. Animal models of atopic dermatitis. *J Invest Dermatol*. 2009; 129:1–31. Review of animal models for atopic dermatitis covering epicutaneous application of sensitizers, transgenic and mice that spontaneously develop AD. [PubMed: 19078977]
51. Huang CH, Kuo IC, Xu H, et al. Mite allergen induces allergic dermatitis with concomitant neurogenic inflammation in mouse. *J Invest Dermatol*. 2003; 121(2):289–93. [PubMed: 12880420]
52. Matsumoto K, Mizukoshi K, Oyobikawa M, et al. Establishment of an atopic dermatitis-like skin model in a hairless mouse by repeated elicitation of contact hypersensitivity that enables to conduct functional analyses of the stratum corneum with various non-invasive biophysical instruments. *Skin Res Technol*. 2004; 10(2):122–9. [PubMed: 15059180]
53. Laouini D, Kawamoto S, Yalcindag A, et al. Epicutaneous sensitization with superantigen induces allergic skin inflammation. *J Allergy Clin Immunol*. 2003; 112(5):981–7. [PubMed: 14610492]
54. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr*. 1985; 107(5):669–75. [PubMed: 4056964]
55. Li XM, Kleiner G, Huang CK, et al. Murine model of atopic dermatitis associated with food hypersensitivity. *J Allergy Clin Immunol*. 2001; 107(4):693–702. [PubMed: 11295660]
56. Oyoshi MK, Murphy GF, Geha RS. Filaggrin-deficient mice exhibit TH17-dominated skin inflammation and permissiveness to epicutaneous sensitization with protein antigen. *J Allergy Clin Immunol*. 2009; 124(3):485–93. 93 e1. [PubMed: 19665780]
57. Nagelkerken L, Verzaal P, Lagerweij T, et al. Development of atopic dermatitis in mice transgenic for human apolipoprotein C1. *J Invest Dermatol*. 2008; 128(5):1165–72. [PubMed: 18049452]
58. Matsuda H, Watanabe N, Geba GP, et al. Development of atopic dermatitis-like skin lesion with IgE hyperproduction in NC/Nga mice. *Int Immunol*. 1997; 9(3):461–6. [PubMed: 9088984]
59. Vestergaard C, Yoneyama H, Murai M, et al. Overproduction of Th2-specific chemokines in NC/Nga mice exhibiting atopic dermatitis-like lesions. *J Clin Invest*. 1999; 104(8):1097–105. [PubMed: 10525048]
60. Aioi A, Tonogaito H, Suto H, et al. Impairment of skin barrier function in NC/Nga Tnd mice as a possible model for atopic dermatitis. *Br J Dermatol*. 2001; 144(1):12–18. [PubMed: 11167677]
61. Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. *J Invest Dermatol*. 2001; 117(4):977–83. [PubMed: 11676841]
62. Barton D, HogenEsch H, Weih F. Mice lacking the transcription factor RelB develop T cell-dependent skin lesions similar to human atopic dermatitis. *Eur J Immunol*. 2000; 30(8):2323–32. [PubMed: 10940923]
63. Hansson L, Backman A, Ny A, et al. Epidermal overexpression of stratum corneum chymotryptic enzyme in mice: a model for chronic itchy dermatitis. *J Invest Dermatol*. 2002; 118(3):444–9. [PubMed: 11874483]
64. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002; 3(7):673–80. [PubMed: 12055625]

65. Yamanaka K, Tanaka M, Tsutsui H, et al. Skin-specific caspase-1-transgenic mice show cutaneous apoptosis and pre-endotoxin shock condition with a high serum level of IL-18. *J Immunol.* 2000; 165(2):997–1003. [PubMed: 10878376]
66. Konishi H, Tsutsui H, Murakami T, et al. IL-18 contributes to the spontaneous development of atopic dermatitis-like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions. *Proc Natl Acad Sci USA.* 2002; 99(17):11340–5. [PubMed: 12151598]
67. Tsukuba T, Okamoto K, Okamoto Y, et al. Association of cathepsin E deficiency with development of atopic dermatitis. *J Biochem.* 2003; 134(6):893–902. [PubMed: 14769879]
68. Haraguchi M, Hino M, Tanaka H, et al. Naturally occurring dermatitis associated with *Staphylococcus aureus* in DS-Nh mice. *Exp Anim.* 1997; 46(3):225–9. [PubMed: 9250484]
69. Roberson ED, Bowcock AM. Psoriasis genetics: breaking the barrier. *Trends Genet.* 2010; 26(9): 415–23. [PubMed: 20692714]
70. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis.* 2005; 64(Suppl 2):ii30–6. [PubMed: 15708932]
- 71•. Schon MP. Animal models of psoriasis: a critical appraisal. *Exp Dermatol.* 2008; 17:8–703. Discusses animal models based upon distinct manipulations of molecular pathways, involving resident cutaneous cell types or immigrating immunocytes, and xenotransplantation of human skin onto immunocompromised animals.
72. Sundberg JP, Beamer WG, Shultz LD, et al. Inherited mouse mutations as models of human adnexal, cornification, and papulosquamous dermatoses. *J Invest Dermatol.* 1990; 95(5 Suppl): 62S–3S.
73. HogenEsch H, Gijbels MJ, Offerman E, et al. A spontaneous mutation characterized by chronic proliferative dermatitis in C57BL mice. *Am J Pathol.* 1993; 143(3):972–82. [PubMed: 8362989]
74. Keith JC Jr, Sainz IM, Isordia-Salas I, et al. A monoclonal antibody against kininogen reduces inflammation in the HLA-B27 transgenic rat. *Arthritis Res Ther.* 2005; 7(4):R769–76. [PubMed: 15987478]
75. Bullard DC, Scharffetter-Kochanek K, McArthur MJ, et al. A polygenic mouse model of psoriasiform skin disease in CD18-deficient mice. *Proc Nat Acad Sci USA.* 1996; 93(5):2116–21. [PubMed: 8700894]
76. Kunstfeld R, Hirakawa S, Hong YK, et al. Induction of cutaneous delayed-type hypersensitivity reactions in VEGF-A transgenic mice results in chronic skin inflammation associated with persistent lymphatic hyperplasia. *Blood.* 2004; 104(4):1048–57. [PubMed: 15100155]
77. Xia YP, Li B, Hylton D, et al. Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. *Blood.* 2003; 102(1):161–8. [PubMed: 12649136]
78. Vassar R, Fuchs E. Transgenic mice provide new insights into the role of TGF- α during epidermal development and differentiation. *Genes Dev.* 1991; 5(5):714–27. [PubMed: 1709129]
79. Li AG, Wang D, Feng XH, et al. Latent TGF β 1 overexpression in keratinocytes results in a severe psoriasis-like skin disorder. *Embo J.* 2004; 23(8):1770–81. [PubMed: 15057277]
80. Guo L, Yu QC, Fuchs E. Targeting expression of keratinocyte growth factor to keratinocytes elicits striking changes in epithelial differentiation in transgenic mice. *Embo J.* 1993; 12(3):973–86. [PubMed: 7681397]
81. Pasparakis M, Courtois G, Hafner M, et al. TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK2. *Nature.* 2002; 417(6891):861–6. [PubMed: 12075355]
- 82••. Zenz R, Eferl R, Kenner L, et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. *Nature.* 2005; 437:7057–369. Reports that the deletion of Jun in mice produces a phenotype similar to human psoriasis.
83. Hirano T, Ishihara K, Hibi M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. *Oncogene.* 2000; 19(21): 2548–56. [PubMed: 10851053]
84. Turksen K, Kupper T, Degenstein L, et al. Interleukin 6: insights to its function in skin by overexpression in transgenic mice. *Proc Nat Acad Sci USA.* 1992; 89(11):5068–72. [PubMed: 1375756]

85. Klaus Wolff, RAJ. Fitzpatrick's color atlas & synopsis of clinical dermatology. 6. Mc-Graw Hill; New York: 2009.
- 86•. Koch PJ, Mahoney MG, Ishikawa H, et al. Targeted disruption of the pemphigus vulgaris antigen (desmoglein 3) gene in mice causes loss of keratinocyte cell adhesion with a phenotype similar to pemphigus vulgaris. *J Cell Biol.* 1997; 137:5–1091. Reports the discovery of desmoglein 3 gene disruption in mice producing a disease similar to pemphigus in humans. [PubMed: 9105032]
87. Koch PJ, Mahoney MG, Cotsarelis G, et al. Desmoglein 3 anchors telogen hair in the follicle. *J Cell Sci.* 1998; 111(Pt 17):2529–37. [PubMed: 9701552]
88. Ganeshan R, Chen J, Koch PJ. Mouse models for blistering skin disorders. *Dermatol Res Pract.* 2010; 2010:584353. [PubMed: 20585602]
89. Bruckner-Tuderman L, McGrath JA, Robinson EC, et al. Animal models of epidermolysis bullosa: update 2010. *J Invest Dermatol.* 2010; 130(6):1485–8. [PubMed: 20463671]
90. Fritsch A, Loeckermann S, Kern JS, et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. *J Clin Invest.* 2008; 118(5):1669–79. [PubMed: 18382769]
91. Roth W, Reuter U, Wohlenberg C, et al. Cytokines as genetic modifiers in K5^{−/−} mice and in human epidermolysis bullosa simplex. *Hum Mutat.* 2009; 30(5):832–41. [PubMed: 19267394]
92. Uitto J. Progress in heritable skin diseases: translational implications of mutation analysis and prospects of molecular therapies. *Acta Derm Venereol.* 2009; 89(3):228–35. [PubMed: 19479117]
93. Heinonen S, Mannikko M, Klement JF, et al. Targeted inactivation of the type VII collagen gene (Col7a1) in mice results in severe blistering phenotype: a model for recessive dystrophic epidermolysis bullosa. *J Cell Sci.* 1999; 112(Pt 21):3641–8. [PubMed: 10523500]
94. Chino T, Tamai K, Yamazaki T, et al. Bone marrow cell transfer into fetal circulation can ameliorate genetic skin diseases by providing fibroblasts to the skin and inducing immune tolerance. *Am J Pathol.* 2008; 173(3):803–14. [PubMed: 18688022]
95. Remington J, Wang X, Hou Y, et al. Injection of recombinant human type VII collagen corrects the disease phenotype in a murine model of dystrophic epidermolysis bullosa. *Mol Ther.* 2009; 17(1): 26–33. [PubMed: 19018253]
96. Tolar J, Ishida-Yamamoto A, Riddle M, et al. Amelioration of epidermolysis bullosa by transfer of wild-type bone marrow cells. *Blood.* 2009; 113(5):1167–74. [PubMed: 18955559]
97. Nishie W, Sawamura D, Goto M, et al. Humanization of autoantigen. *Nat Med.* 2007; 13(3):378–83. [PubMed: 17322897]
98. Nishie W, Shimizu H. Novel animal models for bullous pemphigoid utilized by “humanization of autoantigen”. *Jap J Clin Immunol.* 2009; 32(6):472–7.
99. Morel L. Mouse models of human autoimmune diseases: essential tools that require the proper controls. *PLoS Biol.* 2004; 2(8):E241. [PubMed: 15314657]
- 100•. Furukawa F. Animal models of cutaneous lupus erythematosus and lupus erythematosus photosensitivity. *Lupus.* 1997; 6:2–193. Comprehensive review of animals models of lupus and the effect of sunlight.
101. Perry D, Sang A, Yin Y, et al. Murine models of systemic lupus erythematosus. *J Biomed Biotechnol.* 2011; 2011:271694. [PubMed: 21403825]
102. Cohen PL, Maldonado MA. Animal models for SLE. *Curr Protoc Immunol.* 2003; Chapter 15(Unit 15):20. [PubMed: 18432900]
103. Ghoreishi M, Dutz JP. Cutaneous lupus erythematosus: recent lessons from animal models. *Lupus.* 2010; 19(9):1029–35. [PubMed: 20693196]
104. Furukawa F, Yoshimasu T. Animal models of spontaneous and drug-induced cutaneous lupus erythematosus. *Autoimmun Rev.* 2005; 4(6):345–50. [PubMed: 16081025]
105. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol.* 2005; 26(11):587–95. [PubMed: 16168711]
106. Manetti, EM.; Neumann, E.; Oliver, D., et al. Animal models of scleroderma: from cellular and molecular mechanisms to novel antifibrotic strategies. Springer; London: 2010.
107. Hargis AM, Haupt KH, Prieur DJ, et al. Animal model of human disease. Dermatomyositis Familial canine dermatomyositis. *Am J Pathol.* 1985; 120(2):323–5. [PubMed: 4025513]

108. Lyubomir, A.; Dourmishev, ALD. Animal models of dermatomyositis. *dermatomyositis advances in recognition, understanding and management*. Springer; Berlin Heidelberg: 2009. p. 289-90.
109. Selye H, Gentile G, Jean P. An experimental model of “dermatomyositis” induced by calcephylaxis. *Can Med Assoc J*. 1961; 85:770–6. [PubMed: 13749961]
110. Misfeldt ML, Grimm DR. Sinclair miniature swine: an animal model of human melanoma. *Vet Immunol Immunopathol*. 1994; 43(1–3):167–75. [PubMed: 7856049]
111. Patton EE, Mitchell DL, Nairn RS. Genetic and environmental melanoma models in fish. *Pigment Cell Melanoma Res*. 2010; 23:3–314. Describes how fish can be useful models for melanomagenesis. [PubMed: 19968821]
112. Bardeesy N, Wong KK, DePinho RA, et al. Animal models of melanoma: recent advances and future prospects. *Adv Cancer Res*. 2000; 79:123–56. [PubMed: 10818679]
113. Berghmans S, Jette C, Langenau D, et al. Making waves in cancer research: new models in the zebrafish. *Biotechniques*. 2005; 39(2):227–37. [PubMed: 16116796]
114. Ceol CJ, Houvras Y, White RM, et al. Melanoma biology and the promise of zebrafish. *Zebrafish*. 2008; 5(4):247–55. [PubMed: 19133823]
115. Daya-Grosjean L, Couve-Privat S. Sonic hedgehog signaling in basal cell carcinomas. *Cancer Lett*. 2005; 225(2):181–92. [PubMed: 15978322]
116. Martin P. Wound healing—aiming for perfect skin regeneration. *Science*. 1997; 276(5309):75–81. [PubMed: 9082989]
117. Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med*. 1999; 341(10):738–46. [PubMed: 10471461]
118. Gottrup F, Agren MS, Karlsmark T. Models for use in wound healing research: a survey focusing on in vitro and in vivo adult soft tissue. *Wound Repair Regen*. 2000; 8(2):83–96. [PubMed: 10810034]
119. Xu W, Jong Hong S, Jia S, et al. Application of a partial-thickness human ex vivo skin culture model in cutaneous wound healing study. *Lab Invest*. 2012; 92(4):584–99. [PubMed: 22231737]
120. Shaw TJ, Martin P. Wound repair at a glance. *J Cell Sci*. 2009; 122(Pt 18):3209–13. [PubMed: 19726630]
121. Svedman P, Lundin S, Hoglund P, et al. Passive drug diffusion via standardized skin mini-erosion; methodological aspects and clinical findings with new device. *Pharm Res*. 1996; 13(9): 1354–9. [PubMed: 8893274]
122. Steenfoss HH, Agren MS. A fibre-free alginate dressing in the treatment of split thickness skin graft donor sites. *J Eur Acad Dermatol Venereol*. 1998; 11(3):252–6. [PubMed: 9883438]
123. Chung TY, Peplow PV, Baxter GD. Laser photobiostimulation of wound healing: defining a dose response for splinted wounds in diabetic mice. *Lasers Surg Med*. 2010; 42(9):656–64. [PubMed: 20976805]
124. Nodder S, Martin P. Wound healing in embryos: a review. *Anat Embryol (Berl)*. 1997; 195(3): 215–28. [PubMed: 9084820]
125. Metcalfe AD, Ferguson MW. Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. *J R Soc Interface*. 2007; 4(14):413–37. [PubMed: 17251138]
126. Ferguson MW, O’Kane S. Scar-free healing: from embryonic mechanisms to adult therapeutic intervention. *Philos Trans R Soc Lond B Biol Sci*. 2004; 359(1445):839–50. [PubMed: 15293811]
127. Heng MC. Wound healing in adult skin: aiming for perfect regeneration. *Int J Dermatol*. 2011; 50(9):1058–66. [PubMed: 22126865]
128. Dai T, Kharkwal GB, Tanaka M, et al. Animal models of external traumatic wound infections. *Virulence*. 2011; 2(4):296–315. [PubMed: 21701256]
129. Demidova TN, Gad F, Zahra T, et al. Monitoring photodynamic therapy of localized infections by bioluminescence imaging of genetically engineered bacteria. *J Photochem Photobiol B*. 2005; 81(1):25. Covers the use of mouse models of localized infections caused by genetically engineered bioluminescent bacteria and low light imaging.

130. Dai T, Tegos GP, Zhiyentayev T, et al. Photodynamic therapy for methicillin-resistant *Staphylococcus aureus* infection in a mouse skin abrasion model. *Lasers Surg Med.* 2010; 42(1): 38–44. [PubMed: 20077489]
131. Dai T, Tegos GP, Lu Z, et al. Photodynamic therapy for *Acinetobacter baumannii* burn infections in mice. *Antimicrob Agents Chemother.* 2009; 53(9):3929–34. [PubMed: 19564369]
132. Greenhalgh DG. Models of wound healing. *J Burn Care Rehabil.* 2005; 26(4):293–305. [PubMed: 16006836]
133. King AJ. The use of animal models in diabetes research. *Br J Pharmacol.* 2012; 166(3):877–94. [PubMed: 22352879]
134. Keswani SG, Katz AB, Lim FY, et al. Adenoviral mediated gene transfer of PDGF-B enhances wound healing in type I and type II diabetic wounds. *Wound Repair Regen.* 2004; 12(5):497–504. [PubMed: 15453831]
135. Rees RJ. Animal models in leprosy. *Br Med Bull.* 1988; 44(3):650–64. [PubMed: 3076812]
136. Evans MJ, Levy L. Ultrastructural changes in cells of the mouse footpad infected with *Mycobacterium leprae*. *Infect Immun.* 1972; 5(2):238–47. [PubMed: 4564400]
137. Storrs EE, Binford CH, Migaki G. Animal model of human disease: lepromatous leprosy. *Am J Pathol.* 1978; 92(3):813–16. [PubMed: 686159]
138. Nakano K, Kiyokane K, Benvenuto-Andrade C, et al. Real-time reflectance confocal microscopy, a noninvasive tool for in vivo quantitative evaluation of comedolysis in the rhino mouse model. *Skin Pharmacol Physiol.* 2007; 20(1):29–36. [PubMed: 17035719]
139. Webster GF, Ruggieri MR, McGinley KJ. Correlation of *Propionibacterium acnes* populations with the presence of triglycerides on nonhuman skin. *Appl Environ Microbiol.* 1981; 41(5): 1269–70. [PubMed: 7259157]
140. Zimmerli W, Waldvogel FA, Vaudaux P, et al. Pathogenesis of foreign body infection: description and characteristics of an animal model. *J Infect Dis.* 1982; 146(4):487–97. [PubMed: 7119479]
141. Quenelle DC, Collins DJ, Marciani DJ, et al. Effect of immunization with herpes simplex virus type-1 (HSV-1) glycoprotein D (gD) plus the immune enhancer GPI-0100 on infection with HSV-1 or HSV-2. *Vaccine.* 2006; 24(10):1515–22. [PubMed: 16288820]
142. Oill PA, Galpin JE, Fox MA, et al. Treatment of cutaneous Herpesvirus hominis type 2 infection with 8-methoxypsoralen and long-wave ultraviolet light in guinea pigs. *J Infect Dis.* 1978; 137(6):715–21. [PubMed: 659920]
143. Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control and importance of a not-so-benign virus. *N Engl J Med.* 1983; 309:1362–8. [PubMed: 6314138]
144. Mahalingam R, Traina-Dorge V, Wellish M, et al. Naturally acquired simian varicella virus infection in African green monkeys. *J Virol.* 2002; 76(17):8548–50. [PubMed: 12163574]
145. Felsenfeld AD, Schmidt NJ. Varicella-zoster virus immunizes patas monkeys against simian varicella-like disease. *J Gen Virol.* 1979; 42(1):171–8. [PubMed: 215708]
146. Neal RA. Experimental chemotherapy. Academic Press. 1987; 2:793–845.
147. Baldwin TM, Elso C, Curtis J, et al. The site of *Leishmania major* infection determines disease severity and immune responses. *Infect Immun.* 2003; 71(12):6830–4. [PubMed: 14638769]
148. Beveridge, E. Chemotherapy of leishmaniasis. Academic Press; London: 1963.
149. Laga AC, Murphy GF. The translational basis of human cutaneous photoaging: on models, methods, and meaning. *Am J Pathol.* 2009; 174(2):357–60. [PubMed: 19147830]
150. Mudgil AV, Segal N, Andriani F, et al. Ultraviolet B irradiation induces expansion of intraepithelial tumor cells in a tissue model of early cancer progression. *J Invest Dermatol.* 2003; 121(1):191–7. [PubMed: 12839581]
151. Matsumura Y, Ananthaswamy HN. Molecular mechanisms of photocarcinogenesis. *Front Biosci.* 2002; 7:d765–83. [PubMed: 11897559]
152. Kraemer KH. Sunlight and skin cancer: another link revealed. *Proc Natl Acad Sci USA.* 1997; 94(1):11–14. [PubMed: 8990152]
153. Brash DE, Ziegler A, Jonason AS, et al. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. *J Invest Dermatol Symp Proc.* 1996; 1(2):136–42.

154. Setlow RB. The wavelengths in sunlight effective in producing skin cancer: a theoretical analysis. *Proc Natl Acad Sci USA*. 1974; 71(9):3363–6. [PubMed: 4530308]
155. Johnson FB, Sinclair DA, Guarente L. Molecular biology of aging. *Cell*. 1999; 96(2):291–302. [PubMed: 9988222]
156. Yaar M, Eller MS, Gilchrist BA. Fifty years of skin aging. *J Invest Dermatol Symp Proc*. 2002; 7(1):51–8.
157. Sharma MR, Werth B, Werth VP. Animal models of acute photodamage: comparisons of anatomic, cellular and molecular responses in C57BL/6J, SKH1 and Balb/c mice. *Photochem Photobiol*. 2011; 87(3):690–8. [PubMed: 21332482]
158. Singh T, Chaudhary SC, Kapur P, et al. Nitric oxide donor exisulind is an effective inhibitor of murine photocarcinogenesis(dagger). *Photochem Photobiol*. 2012; 88(5):1141–8. [PubMed: 22364235]
159. Jantschitsch C, Weichenthal M, Proksch E, et al. IL-12 and IL-23 affect photocarcinogenesis differently. *J Invest Dermatol*. 2012; 132(5):1479–86. [PubMed: 22297634]
160. Bernstein EF, Brown DB, Takeuchi T, et al. Evaluation of sunscreens with various sun protection factors in a new transgenic mouse model of cutaneous photoaging that measures elastin promoter activation. *J Am Acad Dermatol*. 1997; 37(5 Pt 1):725–9. [PubMed: 9366817]
161. Krutmann J, Schroeder P. Role of mitochondria in photoaging of human skin: the defective powerhouse model. *J Invest Dermatol Symp Proc*. 2009; 14(1):44–9.
162. Black HS, deGrujl FR, Forbes PD, et al. Photocarcinogenesis: an overview. *J Photochem Photobiol B*. 1997; 40(1):29–47. [PubMed: 9301042]
163. Singh T, Chaudhary SC, Kapur P, et al. Nitric oxide donor exisulind is an effective inhibitor of murine photocarcinogenesis. *Photochem Photobiol*. 2012; 88(5):1141–8. [PubMed: 22364235]
164. Kim TH, Ananthaswamy HN, Kripke ML, et al. Advantages of using hairless mice versus haired mice to test sunscreen efficacy against photoimmune suppressions. *Photochem Photobiol*. 2003; 78(1):37–42. [PubMed: 12929746]
165. Kreuzmann JJ, Buehler EV. A range-finding method for approximating sunscreen efficacy and substantivity using guinea pigs. *J Soc Cosmet Chem*. 1990; (41):275–81.
166. Cole CA, Forbes PD, Ludwigsen K. Sunscreen testing using the mouse ear model. *Photodermatol*. 1989; 6:3–131. Discusses the use of the mouse ear for testing photoprotectants and sunscreens.
167. Tokura Y, Yagi H, Ihda H, et al. Evaluation of ultraviolet-A protection by sunscreen agents using a mouse model of contact photoallergy. *J Dermatol Sci*. 1994; 7(1):39–44. [PubMed: 8193083]
168. Horiki S, Miyauchi-Hashimoto H, Tanaka K, et al. Protective effects of suncreening agents on photocarcinogenesis, photoaging, and DNA damage in XPA gene knockout mice. *Arch Dermatol Res*. 2000; 292(10):511–18. [PubMed: 11142773]
169. Chew S, DeLeo VA, Harber LC. An animal model for evaluation of topical photoprotection against ultraviolet A (320–380 nm) radiation. *J Invest Dermatol*. 1987; 89(4):410–14. [PubMed: 3668283]
170. Loudin AB, Kevin DD. A comparison of sun protective factor (spf) determinations in guinea pigs and humans utilizing artificial light. *Cutan Ocul Toxicol*. 1985; 4(2):135–40.
171. McElwee KJ, Boggess D, Miller J, et al. Spontaneous alopecia areata-like hair loss in one congenic and seven inbred laboratory mouse strains. *J Invest Dermatol Symp Proc*. 1999; 4(3):202–6.
172. McElwee KJ, Hoffmann R. Alopecia areata - animal models. *Clin Exp Dermatol*. 2002; 27(5):410–17. [PubMed: 12190642]
173. Sun J, Silva KA, McElwee KJ, et al. The C3H/HeJ mouse and DEBR rat models for alopecia areata: review of preclinical drug screening approaches and results. *Exp Dermatol*. 2008; 17(10):793–805. [PubMed: 18798913]
174. Kyoizumi S, Suzuki T, Teraoka S, et al. Radiation sensitivity of human hair follicles in SCID-hu mice. *Radiat Res*. 1998; 149(1):11–18. [PubMed: 9421149]
175. Gilhar A, Ullmann Y, Berkutzi T, et al. Autoimmune hair loss (alopecia areata) transferred by T lymphocytes to human scalp explants on SCID mice. *J Clin Invest*. 1998; 101(1):62–7. [PubMed: 9421466]

176. Smyth JR Jr, McNeil M. Alopecia areata and universalis in the Smyth chicken model for spontaneous autoimmune vitiligo. *J Invest Dermatol Symp Proc.* 1999; 4(3):211–15.
177. Sundberg JP, King LE, Bascom C. Animal models for male pattern (androgenetic) alopecia. *Eur J Dermatol.* 2001; 11(4):321–5. [PubMed: 11399538]
178. Powis G, Kooistra K. Doxorubicin-induced hair loss in the Angora rabbit: a study of treatments to protect against the hair loss. *Cancer Chemother Pharmacol.* 1987; 20(3):291–6. [PubMed: 3690802]
179. Nakashima-Kamimura N, Nishimaki K, Mori T, et al. Prevention of chemotherapy-induced alopecia by the anti-death FKN protein. *Life Sci.* 2008; 82(3–4):218–25. [PubMed: 18164732]
180. Paus R, Handjiski B, Eichmüller S, et al. Chemotherapy-induced alopecia in mice. Induction by cyclophosphamide, inhibition by cyclosporine A, and modulation by dexamethasone. *Am J Pathol.* 1994; 144(4):719–34. [PubMed: 8160773]
181. Wikramanayake TC, Amini S, Simon J, et al. A novel rat model for chemotherapy-induced alopecia. *Clin Exp Dermatol.* 2012; 37(3):284–9. [PubMed: 22409523]
182. Wang J, Lu Z, Au JL. Protection against chemotherapy-induced alopecia. *Pharm Res.* 2006; 23(11):2505–14. [PubMed: 16972183]
183. Boehncke WH. The psoriasis SCID mouse model: a tool for drug discovery? Ernst Schering Res Found Workshop. 2005; (50):213–34. [PubMed: 15526945]
184. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005; 366(9494):1367–74. [PubMed: 16226614]
185. Petzelbauer P, Groger M, Kunstfeld R, et al. Human delayed-type hypersensitivity reaction in a SCID mouse engrafted with human T cells and autologous skin. *J Invest Dermatol.* 1996; 107(4):576–81. [PubMed: 8964983]
186. Beehler BC, Chen S, Trampusch KM. Gene expression of retinoic acid receptors and cellular retinoic acid-binding proteins in rhino and hairless mouse skin. *Arch Dermatol Res.* 1995; 287(5):488–93. [PubMed: 7625860]
187. Wong H, Alicke B, West KA, et al. Pharmacokinetic-pharmacodynamic analysis of vismodegib in preclinical models of mutational and ligand-dependent Hedgehog pathway activation. *Clin Cancer Res.* 2011; 17(14):4682–92. [PubMed: 21610148]

Article highlights

- There has been an explosion in the number of transgenic mouse models that are relevant to human skin disease and an increasing number are being used for drug discovery.
- Mouse models of dermatitis can be classified into those relying on some allergic response to antigens and those resulting from genetic manipulation.
- Mouse models of psoriasis include both spontaneous and genetically engineered phenotypes.
- Models of autoimmune diseases such as SLE and SSc using mice and DM using rats and dogs have been developed.
- Skin cancer, especially photocarcinogenesis and photoaging, animal models have employed a wider range of animals including swine and fish (Xiphophorus, medaka fish, and zebrafish).
- As might be expected, the largest range of species has been used in models of wound healing and skin infections, including the chronic wounds found in diabetes.

This box summarizes key points contained in the article.

Figure 1. Structure of the skin

Skin is composed of three layers: epidermis, dermis, and subcutaneous layer. Each layer has various skin appendages such as sweat glands, arrector pili muscle, and sebaceous glands.

Figure 2. Transgenic animal. This figure illustrates the process of formation of transgenic animals by microinjection method.

Figure 3.
The mechanism of Cre/loxP system.

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Figure 5. Psoriasis. Schematic illustration of healthy and psoriatic epidermis

Normal epidermis contains almost 10 cell layers made up of the basal layer, spinous layer, granular layer, and stratum corneum. Stratum corneum is constantly sloughed off and replenished via proliferation in the basal layer. In psoriasis lesions, the granular layer is often absent and corneocytes retain their nuclei [69]. Stratum corneum is thicker and disorganized [69]. Lipids are not secreted in a normal fashion into the extracellular space which leads to a defective water/vapor barrier and the shedding of stratum corneum fragments in large sheets so-called scales or flakes in psoriasis plaques [69]. Components of cornified envelope (CE) are prematurely synthesized in the spinous layer [69]. Connexin 26 (Cx26) is a gap junction protein which is highly upregulated in psoriasis, and transgenic overexpression of Cx26 in mouse epidermis keeps wounded epidermis in a hyperproliferative state while blocking the transition to remodeling. In addition to this, its upregulation also leads to infiltration of immune cells [69].

Figure 6. Phases of wound healing. Key sequence of overlapping phases during healing of a skin wound.

Figure 7. Use of bioluminescence imaging to noninvasively monitor progress of wound and burn infections in real time

A. Partial-thickness skin abrasion infected with methicillin-resistant *S. aureus* [130]. Taken with permission. **B.** Third-degree burn infected with *A. baumannii* [131]. Taken with permission.

Table 1

Characteristics of well-studied SLE-prone mouse strains [100–102].

Mouse Strains	Dermatitis	Photosensitivity	IgG at DEJ	IC-GN	Arteritis	Arthritis
NZB	–	+	+(IgM)	+	–	–
B/W F1	–	+	++(IgG)	+++	–	–
MRL/lpr	++	+++	+(IgG)	+++	+	+
BXSB	–	++	+(IgG)	+++	–	–

IC-GN: Immune complex glomerulonephritis; IgG at DEJ: Immunoglobulins deposit at the dermal – epidermal junction.

Table 2
Animal models of SSc and aspects of SSc pathogenesis reproduced in animal models [105,106].

Model	Skin fibrosis	Vascular	Inflammation	Autoimmune	Key features
<i>Naturally occurring</i>					
Tsk-1 (Tight skin mouse)	+	+	-	+	Duplication of fibrillin gene, elevated expression of CD19
Inbred strain Ucd-200 chickens	+	+	+	+	Visceral vasculopathy, rheumatoid factors, distal polyarthritis
<i>Induced</i>					
Tsk-2 (Type 2 tight skin mouse)	+	-	+	+	Tissue fibrosis, inflammatory cell infiltrate
Bleomycin induced	+	-	+	-	Reactive oxygen species, endothelial cell damage, adhesion molecule expression
Vinyl chloride	+	+	+	-	Microchimaerism, dermal inflammation similar to GvHD
<i>Transplant</i>					
GvHD I (B10.D2. vs BALB/C)	+	+	+	-	Transfer of spleen cells from B10.D2 mice into irradiated BALB/c
GvHD II (B10.D2 vs Rag-2 ^{-/-})	+	+	+	+	Transfer of spleen cells from B10.D2 mice into RAG-2 null mice
<i>Genetic</i>					
TGF-βRII dominant negative	+	-	+	-	Systemic fibrosis, localized inflammation
MRL-lpr-IFN-γR ^{-/-}	+	-	+	+	Lacking IFN-γ receptors, inflammation, systemic fibrosis
Conditional TGF-βRI	+	+	+	-	Conditional expression of TGF-βRI, generalized fibrosis, inflammation
RLX ^{-/-}	+	-	-	-	Relaxing gene knockout mice develop pulmonary, cardiac, renal fibrosis

Table 3

Mouse models of AA [172].

Strain or substrain	Average age at diagnosis (months)	Females with AA	Males with AA	Dorsal and/or ventral skin lesions	Nail lesions	Expression frequency (%)
C3H/HeJ	12	Yes	Yes	Yes	Yes (rare)	20
C3H/HeJBir	12	Yes	Yes	Yes	No	5
C3H/HeN/J	7	Yes	No	Yes	No	<1
C3H/OuJ	9	Yes	No	Yes	No	<1
A/J	7	Yes	Yes	Yes	No	10
HRS/J+/hr	7	Yes	No	Yes	No	<1
CBA/CAHn-Btkxid/J	8	Yes	No	Yes	No	<1
BALB.2R-H2h2/Lil	5	Yes	No	Yes	No	<1

Table 4Types of *in vivo* models to study androgenetic alopecia [177,178].

Mechanism of alopecia occurrence	Species			
Spontaneous androgenic alopecia	Chimpanzees (Pan troglodytes) Stump-tailed Macaque Monkey (<i>Macaca arctoides</i>) South American Uakari (<i>Cacajao Rubicundus</i>)			
Testosterone induced	B6CBAF1 mice and other inbred and hybrid strains	Delayed hair growth in golden Syrian hamsters (<i>Mesocricetus Auratus</i>)	Keratin 5-human androgen receptor transgenic mice (K5-hAR) [160]	Testosterone primed nude mice xenografts
Immune deficiency with or without hormone deficiency	Human to mouse xenografts using immunodeficient mice or immunodeficient mice with hormone deficiencies	Nude (<i>Foxn1</i> mouse – lack T cells)	Severe combined immunodeficiency (<i>Prkd^{sci}</i> – lack B cells) mouse or in combination with steroids	Hypogonadal (<i>hpg</i> : GnRH gene deletion: no serum LH, FSH, or gonadal)

Table 5

CIA mouse models.

Mouse model	Details	Advantages	Disadvantages	Refs.
Doxorubicin-induced angora rabbit		Follows wave pattern	Incomplete hair loss	[178,182]
Neonatal mouse models		Visible hair loss in 2 days	Hair follicles in first postnatal hair growth cycle Growth factors and cytokines may differ from mature animals	[182]
Cytosine arabinoside, cyclophosphamide, Doxorubicin-induced CIA in Sprague Dawley and Wistar rats	7- to 8-day-old rats show spontaneous anagen hair growth for about 1 week		White fur – lack of pigmentation limits study of melanocytes; hair-loss pattern is drug specific	_ENREF_ [164,179]
Adult mouse models				[182]
Etoposide- and cyclophosphamide-induced pigmented Long-Evans rats	Synchronized anagen is induced by clipping			[181]
Black adolescent cyclophosphamide-induced C57BL/6 mouse	Anagen phase is achieved by depilation 8 – 9 days later	Hair follicles have gone through several growth cycles; hair shafts are pigmented		[180]