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Psoriatic Skin Models: A Need for the Pharmaceutical Industry

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1. Introduction

1.1 Skin

Skin is composed of three layers: epidermis, dermis and hypodermis (Sugihara *et al.*, 1991). Epidermis is divided into five layers namely, *stratum basale*, *spinosum*, *granulosum*, *lucidum*, and *corneum* (Bragulla & Homberger, 2009, Nagarajan *et al.*, 2009). The differentiation process implies that keratinocytes are transformed through the different cell layers to reach their complete maturation in the *stratum corneum* (Harding, 2004). In this process, various proliferation and differentiation markers are expressed in a well-orchestrated sequence of events (Fig. 1). When the differentiation process is negatively affected, skin pathologies such as psoriasis can appear (Rashmi *et al.*, 2009, Karlsson *et al.*, 2004).

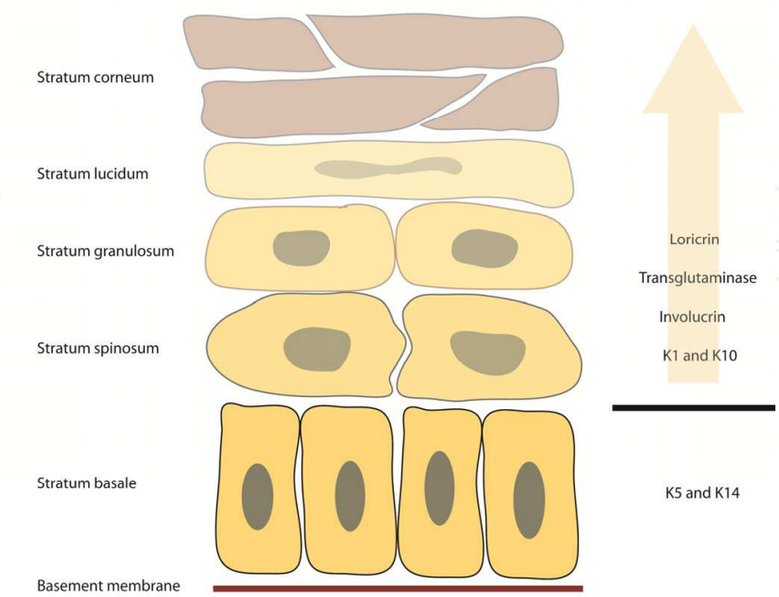

Fig. 1. Differentiation process

1.2 Psoriasis

1.2.1 Prevalence

Psoriasis is a severe skin disease affecting men and women worldwide. It affects about 2 % of the world population (Baker *et al.*, 2008, Wippel-Slupetzky & Stingl, 2009). Previous studies have demonstrated that psoriasis prevalence varies as a result of two factors: (1) geographical localization and (2) ethnic group. Firstly, psoriasis shows a significant geographical variability with the lowest incidence seen at the equator and increasing frequency towards the poles (Kormeili *et al.*, 2004, Krueger & Bowcock, 2005, Lowes *et al.*, 2007) (Fig. 2). Secondly, even if psoriasis is universal, it does not affect all ethnic groups in a similar way. In fact, various studies have demonstrated that psoriasis prevalence can be modified in function of ethnic factors. They established that, in the United States, the prevalence was of 0.5 to 0.7 % in African population compared with 1.4 to 4.6 % for Caucasian population (Schon & Boehncke, 2005). Furthermore, some populations, such as Samoan population (Polynesia), are exempt from psoriasis, whereas other ethnic groups show a high percentage of affected peoples such as observed in Kazach'ye population (12.0 %).

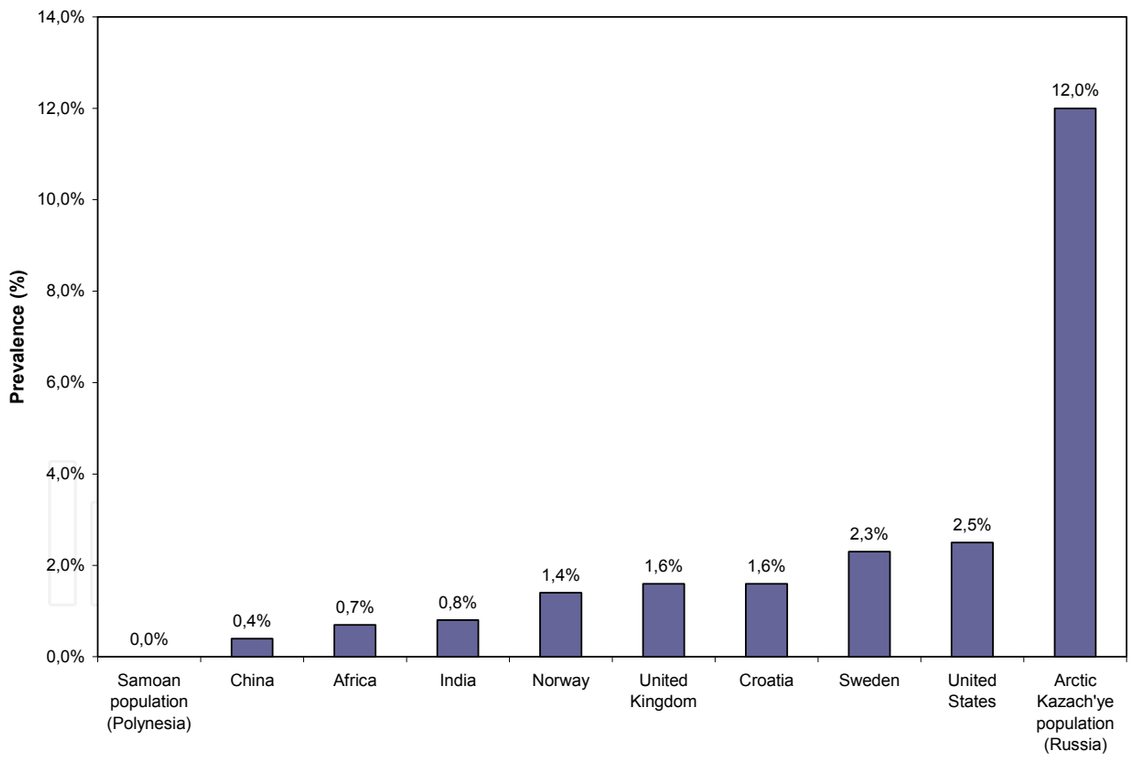

Fig. 2. Worldwide psoriasis prevalence

Psoriasis prevalence shows a significant geographical variability. A lower incidence can be observed at the equator while the frequency increases towards the poles. Studies suggest that the incidence may be related with the time and/or the intensity exposure to the ultraviolet wavelengths of sunlight (Menter & Stoff, 2010).

1.2.2 Physiopathology

Psoriatic skin is characterized by remarkable hyperplasia of the epidermis (acanthosis), loss of the granular layer, increased vascularization in the dermis, and thickening of the cornified layer (hyperkeratosis). Additionally, the incomplete keratinocyte differentiation (parakeratosis) and the leukocyte infiltration in skin are hallmarks of this disease (Tonel & Conrad, 2009).

So far, the pathogenesis of psoriasis constitutes a matter of scientific debate. Controversy exists about whether this disease starts as a primary abnormality of altered keratinocytes or as a result of an altered immune response against an undetermined antigen. According to the first hypothesis, epidermal alterations could be sufficient for the initiation of psoriasis in genetically predisposed individuals. Moreover, it has been demonstrated that the abrogation of JunB/activator protein (AP-1) in epidermal mouse keratinocytes leads to a phenotype that notably mimics psoriasis with inflammation, disturbances in epidermal differentiation and dermal changes, including the expression of chemokines/cytokines, which are able to recruit neutrophils and macrophages in the epidermis (Zenz *et al.*, 2005).

According to the second hypothesis, psoriasis could be a result of an altered immune response to an undetermined antigen. However, it is still not clear where the psoriatic immune response begins. This theory arises from evidences obtained using xenograft psoriatic models, where uninvolved psoriatic skin is transformed into a psoriatic lesion under the action of skin resident cells present in the graft (Boyman *et al.*, 2004, Conrad *et al.*, 2007). The failure to generate a psoriatic lesion after the administration of an anti-CD3 mAb, demonstrated that T cells and not keratinocytes alone were necessary to generate the psoriatic phenotype (Boyman *et al.*, 2004, Conrad *et al.*, 2007). Thus, psoriatic lesions could be initiated by an initial trigger which activates dendritic cells (DCs) and induces their migration to skin-draining lymph nodes. DCs thus prime antigen-specific T cells to differentiate into effector T cells bearing the skin addressing CLA (Cutaneous Lymphocyte Antigen). Activated T cells then traffic to the skin, where they induce together with DCs and other cells, the release pro-inflammatory cytokines, which in turn stimulate keratinocytes to synthesize other cytokines, chemokines and pro-inflammatory molecules, thereby causing the typical epidermal changes observed in psoriasis (Bowcock & Krueger, 2005). Furthermore, migration of T cells in the epidermis seems to be connected with the disturbances of desmosome connection between keratinocytes, thereby contributing to the disruption of epidermal integrity (Krueger, 2002). That could be interpreted by keratinocytes as an injury with a further wound repair response, and the release of cytokines leading to a regenerative epidermal growth.

Psoriasis is considered to be an immune-mediated disease characterized by a predominantly Th1-type cytokine profile in lesional skin with elevated levels of interferon-γ (INF-γ), tumour necrosis factor-alpha (TNF-α), IL-12, and IL-18, among others. Thus, the secretion of the INF-α from DCs and the production of TNF-α by cells of the innate and adaptive immune system are considered to be one of the earliest events leading to psoriasis (Nestle *et al.*, 2005). Cytokines released by T cells, DCs, macrophages and neutrophils such as IL-1, IL-6 and INF-γ have been shown to directly induce epidermal hyperplasia (Krueger, 2002). Additionally, other inflammatory cytokines such as IL-23, have gained attention for their role in psoriasis pathogenesis. IL-23 leads to the production of IL-17 and IL-22, contributing to the enhancement and maintenance of inflammation as well as epidermal proliferation

(Chan *et al.*, 2006, Wolk *et al.*, 2004). Intradermal injection of this IL-23 contributes to the development of epidermal acanthosis in mice (Chan *et al.*, 2006, Zheng *et al.*, 2007). Other evidence supporting its role in psoriasis includes the clinical efficacy of anti-p40 monoclonal antibody (Krueger *et al.*, 2007).

Overall, psoriasis involves a complex interplay between various cells of the immune system and skin, including dendritic cells, T cells, neutrophils, and keratinocytes, which leads to the release of numerous cytokines and chemokines that signal keratinocytes to hyperproliferate and undergo abnormal differentiation (Gottlieb *et al.*, 2003).

1.2.3 Treatment satisfaction: Results of worldwide surveys

Previous worldwide surveys of psoriasis affected individuals have revealed widespread dissatisfaction with available treatments, as well as frustration with current management strategies, thereby demonstrating the need for more appropriate forms of therapy (Nijsten *et al.*, 2005, Stern *et al.*, 2004) and the importance for an improved access for patients to health care services (Klotz *et al.*, 2005, Simpson *et al.*, 2006).

In 1998, a self-administered questionnaire was mailed to the entire membership of the National Psoriasis Foundation in the United States (n=40,350) and followed by a telephone survey of patients with severe psoriasis. Of the 40,350 questionnaires mailed out, a response rate of 43 % was realized. Although 48 % of responders were very or fairly satisfied with psoriasis treatments, a nearly similar number of patients (49 %) reported that they were only somewhat or not at all satisfied (Krueger *et al.*, 2001). Additionally, 46 % of patients responded that their treatment functioned "just somewhat well" or "not well at all" and a high degree of dissatisfaction with the capacity of treatments to control the symptoms was reported. In the case of patients with severe disease, 78 % reported that their treatment did not function well enough, thereby leading them to a frustration with their medications (Krueger *et al.*, 2001). In fact, 32 % of these patients replied that the treatment they received was not aggressive enough. As a consequence, many of the responders (43 %) had tried over-the-counter medications or alternative therapies such as herbs, relaxation or acupuncture in order to control their psoriasis (Krueger *et al.*, 2001). Another survey, conducted with 77 psoriatic patients in Israel also demonstrated that 62 % of patients used complementary and alternative medicines including herbal medicines and nutritional treatments followed by homeopathy and traditional Chinese medicine. The main reasons for complementary and alternative medicines were: the less toxic indications, disappointment with conventional treatments and stress reduction (Ben-Arye *et al.*, 2003).

In order to assess the satisfaction of psoriatic patients with four systemic medications (methotrexate, PUVA-therapy, cyclosporin and acitretin), 1,197 patients were interviewed in the United States between 2001 and 2002 (Nijsten *et al.*, 2005). Of these patients, only 26 % (n=311) indicated the use of these systemic treatments for their psoriasis. Less than 40 % of these patients were very satisfied with their treatment, while a comparable proportion indicated being dissatisfied. Low levels of satisfaction were related with treatment resistance, toxicity, convenience, costs and unrealistic patients' expectations (Nijsten *et al.*, 2005). Patients were more satisfied with methotrexate and PUVA-therapy than with acitretin and cyclosporine. Furthermore, PUVA-therapy had the highest satisfaction rate and cyclosporine the lowest compared with other therapies.

In 2002, the European Federation of Psoriasis Patient Associations (EUROPSO) carried out a Europe-wide survey investigating quality of life of psoriatic patients, as well as their satisfaction with available treatments (Dubertret *et al.*, 2006). Self-administered questionnaires were thus mailed to members of psoriasis associations in Germany, Belgium, Finland, France, Czech Republic, Italy and Netherlands. From 18,386 responders, 17,990 had psoriasis. At the time of the survey, 32 % of all participants used a topical treatment, 17 % a systemic treatment and 13 % phototherapy treatment. Although many patients were satisfied with the information and care offered by their physicians (40 % highly satisfied), available treatment modalities were less satisfactory, with over 70 % reporting low or moderate satisfaction. Higher satisfaction (score of 8–10) was observed for treatments with methotrexate (30 %), cyclosporin (28 %) and fumarates (26 %) followed by PUVA-therapy (38 %). Lower satisfaction (score of 1–4) was observed for tazarotene (42 %) and etretinate (38 %). Responders (50 %) reported that the time consumed during therapies was the most troublesome aspect, followed by ineffectiveness of treatments (32 %). Patients with severe psoriasis reported side effects as a problem (31 %), whereas only 23 % of patients with mild psoriasis considered this aspect (Dubertret *et al.*, 2006). Furthermore, another survey conducted in 2003 with 301 psoriatic patients in Europe, also demonstrated that 42 % of patients were dissatisfied with their treatment (Christophers *et al.*, 2006). Lack of satisfaction was lower among the patients receiving treatment with more than one agent, and in those who had more frequent psoriasis relapses, demonstrating the high need for safe and effective therapies for management of this disease (Christophers *et al.*, 2006).

Patients diagnosed with psoriasis in the United States between 2006 and 2007 were contacted to complete an online survey ("Psoriasis Patient Study Wave 1") related to their psoriasis diagnosis, treatment and treatment satisfaction (total of patients=1,006). Of those who had ever taken a prescription (topical, phototherapy, systemic oral or biologics, n=557), 31.8 % (n=177) reported that their current treatment was not able to satisfactorily clear their psoriasis. When patients were separated by treatment, 20.8 % (n=33) of those using biologics, 31.1 % (n=33) of those using systemic oral, 46.4 % (n=13) of those using phototherapy, and 34.2 % (n=163) of those using topical treatments reported that their current treatment was not able to satisfactorily clear their psoriasis. Patients with severe disease were less satisfied than those with mild and moderate disease (47.9 % *vs.* 32.9 % *vs.* 27.6 % respectively) (DiBonaventura *et al.*, 2010).

An online Canadian survey conducted in December 2007 with 514 patients diagnosed with moderate, severe and very severe plaque psoriasis demonstrated that awareness of available treatment options ranged from 98 % for topical treatments to 75 % for phototherapies, 49 % for oral treatments and 35 % for injectable medications. Satisfaction with treatments were generally low, and only 24 % of patients reported to be "very satisfied" with their current therapy. Satisfaction decreased with the increase of psoriasis severity, 39 % of patients with mild/very mild psoriasis reported to be ''very satisfied'', compared with 16 % of those diagnosed with moderate/severe/very severe psoriasis (Wasel *et al.*, 2009). In this survey, dissatisfaction with the efficacy of antipsoriatic treatment was highlighted by the majority of patients (68 %) reporting that ''No medication works really well for my psoriasis''. Additionally, patients with severe psoriasis more frequently complained that "medication was very ineffective for my psoriasis" compared to those less affected (49 %, 69 % and 77 % for respondents with 0–2 %, > 3%, and > 10% of body surface area (BSA) involvement, respectively) (Wasel *et al.*, 2009). Additionally, most affected patients were concerned about

side effects from medication to treat psoriasis (54 %, 64 % and 69 % of psoriatic patients with 0–2 %, > 3% and > 10% BSA involvement, respectively). Patients also manifested that the reasons for treatment discontinuation were as following: lack of efficacy (60 %), inconvenience (23 %) and improvement of symptoms (22 %), side effects (20 %), cost (14 %) and doctor's advice (14 %) (Poulin *et al.*, 2010).

Overall, results of worldwide surveys demonstrate that a substantial proportion of psoriatic patients are highly dissatisfied with current therapies, particularly those with greater psoriasis severity. A perceived lack of efficacy of available treatments suggests the importance of the development of more relevant treatments, in order to allow the establishment of more individualized therapies.

2. Challenges for antipsoriatic drug development

The most significant challenge for antipsoriatic drug development is to provide safe and effective long-term management of this disease. In general, a conventional vision of this process starts with the study of disease in relevant model systems, in order to determine cellular and molecular mechanisms involved in pathogenesis. Afterwards, new therapeutic approaches are developed in these models before clinical trials in humans (Guttman-Yassky & Krueger, 2007). The comprehension that psoriasis is an immune-mediated disease, which involves a complex interplay of T cells, natural killer cells, dendritic cells, macrophages and other leukocytes, has led to the development of new biological treatments. The positive results obtained with these agents have expanded our understanding on psoriasis pathogenesis. However, many questions remain regarding psoriasis pathogenesis, and other medications should be developed to offer individualized treatments able to improve patient's quality of life. Some of the challenges for this field include the improvement of efficacy and safety of new drugs, the solution of problems related to formulation/administration/costs of new agents, and the development of more relevant psoriatic skin models.

2.1 Efficacy

Many psoriatic patients are unresponsive to current therapies or have aggressive disease that is not addressed by current approaches. The determination of relevant biomarkers directly related to psoriasis pathogenesis to be targeted with effective treatments could allow quantitative assessment of treatment response (Rashmi *et al.*, 2009).

2.2 Safety

The challenge of improving the safety of new antipsoriatic drugs is a very important aspect for long-term therapies, and can be overcome through the understanding of the toxicity mechanisms of new agents at early stages of drug development. Unfortunately, this is not always feasible during the drug development process, and the "safety question" should respond to what constitutes an acceptable risk. Thus, it is important to carefully analyse the risk/benefit rate of new antipsoriatic agents, mainly in the case of severe disease.

2.3 Practical issues

In the case of drugs approved for clinical use, their specific immunogenicity, costs, patient access and inconveniences for administration should be considerate. Other challenges

include the optimization of the new drug delivery to give maximum effects to its intended biological targets.

2.4 Development of more relevant psoriatic skin models

Maybe the most important challenge for antipsoriatic drug development is the inexistence of validated *in vivo* and *in vitro* skin models. Psoriasis is a complex disease in which interactions with 30 or more upregulated cytokines and chemokines implies the formation of interactive circuits that are not completely reproduced by *in vivo* and *in vitro* models. In the case of animal models, which are very important in pre-clinic stages of drug development, no one can fully mimic the genomic signature of this disease in which expression than more of 1,300 genes is altered (Guttman-Yassky & Krueger, 2007). Other problems are related to the fact that murine skin is different from human skin, and often the immune infiltrates are less intense and contain different mixtures of leucocytes compared with psoriatic plaques (Gudjonsson *et al.*, 2007). Furthermore, animal models of epidermal hyperplasia are not selective enough, being also used for the study of other diseases, such as atopic dermatitis, even when different inflammatory genes are implied in these two diseases. Thus, it is not a surprise that targeted therapies such as the antibody efalizumab, are effective in both diseases (Farshidi & Sadeghi, 2006). The lack of representative *in vivo* and *in vitro* skin models could also be related to failures of clinical trials at late stages. Hence, some psoriatic models are of questionable value for the development of selective antipsoriatic treatments. A detailed explanation of these models will be provided in subsequent sections.

3. *In vivo* and *in vitro* psoriatic skin models

3.1 *In vivo* models

3.1.1 Spontaneous mutations

Psoriasis is a typical human skin disease. Even if spontaneous mutation models do not exhibit every features found in psoriasis, various pathology-like characteristics can be observed, including hyperkeratosis and scaly formation (Mizutani *et al.*, 2003). Hundred of these spontaneous mutation models have been described in the literature (Sundberg *et al.*, 1990), but no one shows all the characteristics of psoriasis. However, these models can be really practical for studying individual characteristics such as hyperkeratosis (Schon, 2008). A comparison between the characteristics observed in the three major models of spontaneous mutations is presented in table 1.

3.1.2 Xenotransplantation

Animal models based on transgenic technology have been used extensively to study the pathogenesis of various skin diseases, including psoriasis (Raychaudhuri *et al.*, 2001, Jean & Pouliot, 2010). Xenotransplantation approach consists of grafting a piece of *in vivo* psoriatic skin (or an *in vitro* psoriatic substitute) on a genetically modified mouse. Currently, three major models are used: athymic nude mice (Fraki *et al.*, 1983), severe combined immunodeficient mice (SCID) (Raychaudhuri *et al.*, 2001), and spontaneous AGR129 model (Boyman *et al.*, 2004). The main difference between each model is the immunological potential of the immune system. Athymic nude mice have no thymus and therefore no T cells, whereas severe combined immunodeficient mice have no T and no B cells

Model	Characteristics		References
	Psoriasis-like	Psoriasis-unlike	
Homozygous *asebia* ($Scd1^{ab}/Scd1^{ab}$)	Epidermal acanthosis Increased dermal vascularization Dermal infiltrate (mast cells and macrophages)	Alterations of the cutaneous lipid metabolism different from psoriasis Lack of T cells and neutrophils	(Schon, 2008, Zheng *et al.*, 1999)
Flaky skin mice (Ttc^{fsn}/Ttc^{fsn})	Best spontaneous model of psoriasis described Proliferation and hyperkeratosis of stratified squamous epithelia Positive Koebner reaction after tape-stripping	Comprises aspects not find in psoriasis Lack of the immunological side	(Sundberg *et al.*, 1990, Danilenko, 2008, Stratis *et al.*, 2006, Sundberg *et al.*, 1994, Schon, 1999)
Spontaneous chronic proliferative dermatitis mutation ($Sharpin^{cpdm}/Sharpin^{cpdm}$)	Hyperproliferative skin Infiltration of inflammatory cells in the skin Dilation of blood vessels in the dermis	Lack of T cells	(Schon, 1999)

Table 1. Examples of spontaneous mutation models and their characteristics

(Raychaudhuri *et al.*, 2001). As for AGR129 model, it is characterized by the absence of T and B cells and by the presence of immature natural killer (NK) cells, less cytotoxic than mature NK cells (Boyman *et al.*, 2004). A weaker system is potent to dwell skin transplants for a longer time on a compromised mouse upon rejection. Thus, the amount of transplant rejection is reduced in the AGR129 model compared to the others. Boyman *et al.* demonstrated that human uninvolved psoriatic skin grafted onto AGR129 mice spontaneously developed psoriatic plaques without the injection of any activated immune cells or any other exogenous factor, suggesting that uninvolved psoriatic skin is not exactly comparable to the normal human skin of healthy patients (Boyman *et al.*, 2004, Gudjonsson *et al.*, 2007, Jean & Pouliot, 2010). However, the absence of an inflammatory system could be a significant weakness of these models, since the importance of the immunology has been described by many research groups.

3.1.3 Genetically modified models

Development of rat and mouse transgenic models was an important step in the field of *in vivo* models. These genetically modified animals allow the observation of psoriasis-like

characteristics in rodents following the overexpression or underexpression of cytokines (or enzymes) (Bullard *et al.*, 1996, Danilenko, 2008, Keith *et al.*, 2005). It is important to note that psoriasis is a multisystemic skin disease, and that transgenic models consider only a single gene at the time. Thus, even if these models are interesting to observe isolated psoriasis-like features, they do not allow the study of all the characteristics of the pathology. There exist a broad variety of genetically modified *in vivo* models. An exhaustive list can be seen in table 2 (Jean & Pouliot, 2010).

Model	Epidermal thickness	Abnormal differentiation	Increased vascularization	Epidermal T cell infiltration	References
Targeting the immune system					
HLA-B27/β2 microglobulin rat	+	+	+	+	(Keith *et al.*, 2005, Breban *et al.*, 1996)
Hypomorphic CD18	+	+	+	+	(Bullard *et al.*, 1996, Kess *et al.*, 2003)
αE (CD103)	+	+	?	+	(Schon *et al.*, 2000)
K14/p40	+	?	?	+	(Kopp *et al.*, 2001)
Targeting vascular endothelium					
pTek-*tTA*/Tie2	+	+	+	+	(Voskas *et al.*, 2005)
K14/VEGF	+	+	+	+	(Xia *et al.*, 2003)
Targeting epidermal proteins					
K5/Stat3C	+	+	+	+	(Sano *et al.*, 2005)
IKK2	+	+	?	-	(Pasparakis *et al.*, 2002)
c-Jun/JunB	+	+	+	+	(Zenz *et al.*, 2005)
K14/KGF	+	+	+	-	(Guo *et al.*, 1993)
K14/TGF-α	+	+	?	Some animals	(Vassar & Fuchs, 1991)
K14/IL-20	+	+	-	-	(Blumberg *et al.*, 2001)
K14/amphiregulin	+	+	+	+	(Cook *et al.*, 1997)
K14/IL-1α	+	+	-	?	(Groves *et al.*, 1995)
K14/IL-6	+	-	-	-	(Turksen *et al.*, 1992)
K10/BMP-6	+	+	+	+	(Blessing *et al.*, 1996)
Involucrin/integrins	+	+	+	+	(Carroll *et al.*, 1995)
Involucrin/MEK1	+	+	?	+	(Hobbs *et al.*, 2004)
Involucrin/amphiregulin	+	+	+	+	(Cook *et al.*, 2004)
Involucrin/IFN-γ	+	+	+	-	(Carroll *et al.*, 1997)
Chymotryptic enzyme	+	+	?	+	(Hansson *et al.*, 2002)

Table 2. *In vivo* genetically modified models of psoriasis

3.2 *In vitro* models

3.2.1 Monolayer

By using only a small skin biopsy, monolayer techniques allow the attainment of a large number of cells (normal or pathological) supporting the production of many experiments. In monolayer models, only one cell type is studied. Thus, keratinocytes (or fibroblasts) can be used to test different conditions or to observe psoriatic skin features such as hyperproliferation or abnormal differentiation of keratinocytes. These models allow the isolation of one cell type for step by step dissection of the implied mechanisms. Even if it was not possible to observe direct interaction between cell types, these models allowed the discovery of many interesting facts about psoriasis, and favoured a better understanding of the pathology (Jean & Pouliot, 2010).

3.2.2 Collagen gels

Despite the absence of a complete *in vitro* model allowing the observation of interactions between different cell types, such as keratinocytes and fibroblasts, some teams have developed specialized techniques which imply an exogenous matrix: the collagen gel.

3.2.2.1 Organ culture

Some teams decided to put down complete skin biopsies on collagen gel, containing fibroblasts, to observe cell proliferation. Total surface recovered by keratinocytes was used to calculate cell proliferation percentage (Saiag *et al.*, 1985). Higher keratinocyte proliferation values were obtained in the presence of psoriatic fibroblasts (Saiag *et al.*, 1985). Furthermore, this model led to the conclusion that normal fibroblasts are unable to suppress the hyperproliferative growth of psoriatic keratinocytes, and that hyperproliferation of normal epidermis can be induced both by uninvolved and involved psoriatic fibroblasts (Saiag *et al.*, 1985, Jean & Pouliot, 2010).

3.2.2.2 Models using many cellular types

Other teams developed skin substitutes composed of two cell types, in order to observe the effects of psoriatic keratinocytes on fibroblasts and *vice versa*. In a global way, these models consist of isolating normal and pathological cells from a small biopsy. Fibroblasts are extracted from dermis, expanded and seeded in collagen gel. Keratinocytes are extracted in a similar way and are placed on the pre-prepared collagen gel (Konstantinova *et al.*, 1996). Barker *et al.* developed and characterized an *in vitro* psoriatic skin model using collagen gel. This model was very representative of the pathology (Barker *et al.*, 2004). In fact, they have demonstrated that the model kept many characteristics of psoriasis such as hyperproliferation and abnormal differentiation of keratinocytes, augmentation of the interleukin 6 and 8 concentrations, as well as the overexpression or underexpression of some proliferation, differentiation and inflammatory markers observed in psoriatic skin. Researchers concluded that involved and uninvolved skins seem to have the same pathological characteristics as psoriatic human skin (Barker *et al.*, 2004, Jean & Pouliot, 2010). Barker, Konstantinova and Saiag models are interesting *in vitro* models for studying psoriasis, but they are produced with a contractile exogenous material (collagen gel).

3.2.3 Self-assembly approach

Facing the absence of exogenous material-free models, our group developed a new pathological skin model to study psoriasis *in vitro* by using the self-assembly approach (Michel *et al.*, 1999) (Fig. 3). Briefly, normal and pathological fibroblasts are thawed and cultured with ascorbic acid for a period of time of four weeks. Then, dermal sheets are produced and removed from flasks. Two fibroblast sheets are superimposed to form a new dermal equivalent. Seven days later, normal or pathological keratinocytes are seeded on the dermal equivalent to obtain a new epidermal equivalent. After another 7 days of culture, the substitutes are raised to the air–liquid interface to favour cell differentiation and stratification. Finally, biopsies are taken after 21 days of culture at the air–liquid interface, and samples are analyzed using histological, immunohistochemical, physico-chemical or permeability techniques (Jean *et al.*, 2009).

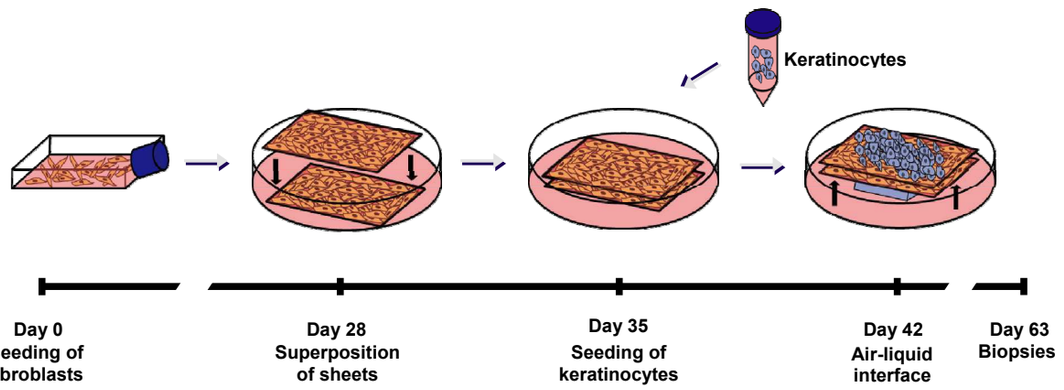

Fig. 3. The self-assembly approach for the production of skin substitutes

Schematic representation of the various steps of skin substitutes production in function of time. Reproduced and modified from Jean *et al.*, 2010 according to the copyright policy of the publisher. © 2010 InTech.

In 2009, Jean *et al.* showed that self-assembled skin substitutes partially maintained psoriasis-like features such as a thick epidermis, hyperproliferation as well as abnormal cell differentiation of epidermal cells (Jean *et al.*, 2009). In 2011, they demonstrated for the first time that pathological substitutes produced by the self-assembly approach can be treated with an anti-psoriatic molecule and react positively to the treatment such as observed in psoriatic skin *in vivo*. This functional study suggests that the self-assembled skin substitutes could be useful to better understand the mechanisms through which retinoic acid regulates cellular physiology in psoriatic skin, and could become an effective and innovative dermopharmaceutical tool for the screening of new treatments (Jean *et al.*, 2011).

4. Conclusion

Psoriasis is characterized by the presence of physical and psychological pains, which can severely affect the quality of life of psoriatic patients. Currently, a broad spectrum of anti-psoriatic treatments, both topical and systemic, is available for the management of psoriasis. These treatments only allow to control psoriasis without curing it. Challenges for antipsoriatic-drugs development are numerous, and the pharmaceutical industry strongly

needs highly predictive *in vivo* and *in vitro* models to improve the success rate of the development of new drugs. Effectively, the lack of representative *in vivo* and *in vitro* models could be related with failures of clinical trials. Thus, the elaboration of these models represents a key component in the fight against psoriasis.

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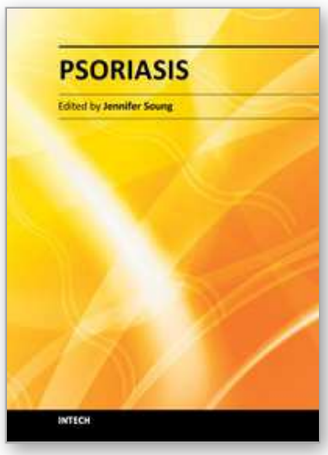

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