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## Future Perspectives in the Treatment of Psoriasis

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### Abstract

All available antipsoriatic therapies are of symptomatic character. Treatments established so far are limited in their use due to side effects or lack of efficacy resulting in poor quality of life for affected people. Development of new therapeutic approaches would not only broaden our armamentarium against psoriasis, but could also increase our understanding of the pathogenesis of this disease. In brief, 2 main targets represent attractive candidates, either the keratinocyte itself or the immune system. Promising therapeutic strategies include: (1) the search for new psoriasis susceptibility genes and their resulting phenotypes; (2) the interference with certain parts of cell signaling pathways that are involved in inflammatory processes; (3) the inhibition or elimination of activated T lymphocytes, e.g. by blocking of costimulatory signals or by deviation of a pathogenic immune response into a nonpathogenic one; (4) the blockade of proinflammatory cytokines; (5) the inhibition of leukocyte extravasation or trafficking; (6) the inhibition of angiogenesis. Some of these strategies are in phase 2 trials, others have already reached phase 3 status and are close to being approved by medicine agencies, and some are still visions of the future. This book chapter will give an overview of these new treatment strategies.

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Psoriasis is a common chronic inflammatory skin disorder that affects about 2–3% of the world's population. Depending on the degree of severity and activity of the disease, several topical, physical and systemic therapies are available nowadays.

They either target selective immune mechanisms involved in the disease process or are of auxiliary value. Up to now, all currently available therapies are only symptomatic. For localized and mild forms, topical corticosteroids, vitamin D<sub>3</sub> analogs (calcipotriene), retinoids (tazarotene), tars, anthralin and phototherapy are good therapeutic options. Conventional systemic therapies for severe psoriasis include oral retinoids, methotrexate, cyclosporine and PUVA. These established treatments are often sufficient for disease control, but all of them have their limitations. After long-term use 'escape mechanisms' may occur, resulting in loss of response. Alternatively,

a high potential for considerable adverse effects impairing quality of life may force treating physicians to terminate otherwise effective therapies. In the last years, an increased understanding of the pathophysiology of psoriasis has enabled the development of new targeted biological agents. Although these biologics have ushered in a new therapeutic era by revolutionizing the management of severe psoriasis, our long-term experience with these compounds is still limited, both with regard to efficacy and, more importantly, safety. Additionally, loss of efficacy as well as disease unresponsiveness have also been observed for biologics. For that reason, there is a need for new highly effective and safe therapy options for both topical and systemic use. If one takes the complex pathogenesis of psoriasis into consideration, there are diverse targets for therapeutic interventions. This book chapter aims at summarizing new treatment approaches for psoriasis (table 1).

The pathogenesis of this highly inflammatory disease has long been a matter of debate. Controversy exists as to whether psoriasis starts as a primary abnormality in keratinocytes or is the consequence of an altered immune response against an as yet undefined antigen. The first hypothesis claims that 1 or more genetically determined molecular lesions in indigenous cells of the skin (e.g. keratinocytes) induce an altered activation of these cells. In fact, aberrant signaling and transcription factor activation can serve as a reasonable explanation for the defective growth control and differentiation of psoriatic keratinocytes [1], as well as for the occurrence of an inflammatory tissue response being induced by cytokines produced by activated keratinocytes such as IL-1, IL-6, IL-8, IFN- $\gamma$ , TNF- $\alpha$ , TGF- $\alpha$  and granulocyte/macrophage colony-stimulating factor [2]. This could result in an antigen-independent activation, adhesion and attraction of T lymphocytes. Zenz et al. [3] developed a mouse model, in which the elimination of the central transcription factor JunB in epidermal keratinocytes leads to a phenotype that greatly resembles psoriasis including arthritis. There was not only a disturbed epidermal differentiation, but also dermal changes including inflammation and expression of chemokines/cytokines recruiting neutrophils and macrophages. From a conceptual viewpoint, it is certainly remarkable that epidermal alterations are sufficient to initiate both skin lesions and arthritis in psoriasis. JunB is a gene localized in PSORS6, 1 of the at least 20 psoriasis susceptibility regions that have been identified so far.

According to the second hypothesis, psoriasis is the result of an abnormal immune response to an as yet undefined autoantigen or microbial antigens, e.g. streptococcal, with molecular homology to certain self proteins [4]. It is not yet clear where the psoriatic immune response begins. Lymphoid tissues such as tonsils are certainly a good candidate as identical TCR patterns have been described in tonsillar T cells after streptococcal infection and skin-homing T cells in peripheral blood and skin. On the other hand, nonlesional psoriatic skin contains a small reservoir of pathogenic T cells that can be expanded by stimuli derived from certain types of cutaneous dendritic cells [5]. In any event, one can assume that T cells attracted to and/or expanded in the skin do not only cause inflammation, but also, through keratinocyte activation,

**Table 1.** New systemic therapeutic perspectives in the treatment of psoriasis

Strategies	Areas of interest
Inhibition of growth factors	tyrosine kinase inhibitors
P38 MAPK inhibitors	BMS-582949
JAK/STAT pathway inhibitors	JAK3 antibody (CP-690,550)
PDE-4 inhibitors	apremilast (CC-10004)
Protein kinase C inhibitor	AEB071
Inhibition of T cell activation/elimination of activated T cells	CD3 antibody (Hum29) CD4 antibody (OKT4a) IL-2-diphtheria toxin fusion protein (DAB398IL-2, Ontak®) calcineurin inhibitors (ISA 247, Voclosporin®)
Blockade of costimulatory signals	CTLA-4 Ig (abatacept, Orencia®, BMS-188667) CD80 antibody (IDEC-114, galiximab)
Deviation of Th1 and Th17 to Th2 responses	IL-4 IL-10 (Tenovil™) IL-12/23 p40 antibodies (CNTO 1275, ustekinumab, Stelara™, ABT-874)
Inhibition of proinflammatory cytokines	TNF- $\alpha$ (golimumab) INF- $\gamma$ (fontolizumab, HuZAF®) INF- $\alpha$ (MEDI-545) IL-6 antibody (tocilizumab, Actemra®) IL-8 antibody (HuMab 10F8) IL-18/IL-1 release inhibitor P2x7 (CE-224,535)
Blocking of leukocyte extravasation/trafficking	Pan-selectin antagonist (bimosiamose, TBC1269, efomycine)
Antiangiogenesis	VEGF antagonist (AE-941, Neovastat®)

enhanced production of growth factors resulting in acanthosis, parakeratosis and neoangiogenesis.

### Interference with Upregulated Signal Transduction Pathways in Psoriatic Skin

In normal skin, keratins 5/14 are found in the basal layer, whereas in psoriatic skin they reach the spinous layer [6]. In contrast, keratins 10/1, which are normally expressed in suprabasal keratinocytes, are considerably reduced. Keratins 6/16, which usually play an essential role in wound healing, are both strongly expressed in psoriatic

epidermis. Classic therapies such as dithranol, tar, vitamin D derivatives, retinoids and methotrexate are said to inhibit keratinocyte hyperproliferation, beside other effects. All these therapies have their limitations, either concerning their efficacy, applicability, side effects and resulting quality of life issues. Therefore, we are seeking innovative strategies.

Due to an increased understanding of signaling pathways that are operative in cell cycle regulation and gene transcription [7], new potential targets in keratinocytes and/or inflammatory cells could be identified.

#### *Inhibition of Growth Factors (e.g. Epidermal Growth Factor) and Subsequent Activation of Receptor Tyrosine Kinases*

The epidermal growth factor receptor and its ligands represents one of the main switches regulating central biological processes such as cell division, cell death, differentiation and tumorigenesis [for a review, see 8]. Overexpression of multiple EGRF ligands is also a hallmark of the psoriatic epidermis. To date, there exist individual case reports of clinical improvement of psoriasis with tyrosine kinase inhibitors (e.g. imatinib) that were given primarily against various types of cancer [9]. However, prospective, randomized studies are still missing.

#### *p38 MAPK Inhibitors*

Certain signals from the cell surface are transduced into changes in cell cycle kinetics and/or gene expression via intracellular protein cascades such as MAPK [10]. Four classical MAPK have been described [11]: the extracellular signal-regulated kinases 1 and 2 (ERK 1/2), the p38 MAPK, the c-jun amino-terminal kinases and atypical MAPK (ERK 3 and ERK 5). P38 MAPK cascades are involved in the production of TNF by macrophages in response to stimulation with lipopolysaccharides [12] and are activated in many cell types, also keratinocytes, in response to TNF signaling. Johansen et al. [13] showed that both ERK 1/2 and p38 activity are increased in psoriatic skin, indicating a possible role in the development of the disease.

Several p38 inhibitors have been tested in clinical trials that were discontinued because of considerable side effects such as CNS and liver toxicity [14]. New p38 MAPK inhibitors that are unable to cross the brain-blood barrier are now being tested in clinical trials. As an example, the study using the compound BMS-582949 (Bristol-Myers-Squibb) is currently recruiting participants for a placebo-controlled phase II study. There are 4 treatment groups, either receiving tablets containing 10, 30, 100 mg BMS-582949 or placebo. The estimated study completion is December 2009.

### *JAK/STAT Pathway Inhibitors*

JAK are a small family of protein tyrosine kinases that are linked to cytokine receptors and consist of JAK1, JAK2, JAK3 and the tyrosine kinase-2. JAKs are activated by the hematopoietic cytokine family and by interferons that target the STAT family of transcription factors. Unlike other JAKs, which are widely expressed and bind several cytokine receptors, JAK3 is an attractive candidate for drug development since it has limited tissue distribution and is activated by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [15]. The first orally available selective JAK3 antibody (CP-690, 550) effectively prevented transplant rejection in animal models and inhibited delayed hypersensitivity. Its role in treating autoimmune diseases has yet to be evaluated.

STAT are a family of latent cytoplasmatic proteins involved in transmitting extracellular signals to the nucleus. Among the STAT, targeting STAT 3 may be of particular therapeutic benefit. STAT3 is involved in the regulation of cell migration, survival and proliferation, and is activated in psoriasis. Sano et al. [16] described a transgenic mouse model with keratinocytes expressing constitutively active STAT3. These mice develop a phenotype resembling psoriasis after wounding or even spontaneously. The onset of psoriatic lesions could be inhibited by abrogation of the STAT3 function, and established lesions could be reversed.

### *Phosphodiesterase 4 Inhibitors*

The phosphodiesterases (PDE) are enzymes which specifically degrade the phosphodiester bond in the second messenger molecules cAMP and cGMP. So far, 11 different PDE have been described. Among them, PDE4 is the major cAMP-metabolizing enzyme found in many inflammatory cells such as T cells, macrophages, neutrophils and eosinophils, but is also expressed in keratinocytes and fibroblasts. Since the late 1980s, PDE4 inhibitors have been under investigation as anti-inflammatory therapies against asthma and chronic obstructive pulmonary disease. So far, none of the agents developed have reached the market, mainly due to a lack of efficacy caused by the narrow therapeutic window of these inhibitors. Dose-limiting side effects like nausea, diarrhea, vomiting and abdominal pain are the main obstacle. Due to the broad anti-inflammatory activity of PDE4 inhibitors, their possible use in the treatment of atopic dermatitis and psoriasis was examined. Some of them showed strong anti-inflammatory action in models of allergic and irritant skin affections. Recently presented results from a randomized 260-patient multicenter study demonstrated that 24.4% of patients treated with 20 mg b.i.d. of oral apremilast (CC-10004) had a PASI 75 after 84 days, compared to 10.3% in the placebo arm [presented at the 66th Ann Meet Am Acad Dermatol, Feb 2008]. Based on these promising results, the dosage will be raised to 30 mg b.i.d. and the duration of dosing will be expanded up to 6 months.

### *Protein Kinase C Inhibitors*

AEB071 is an attractive tool, which is an inhibitor of protein kinase C (PKC) and consequently blocks early T cell activation as measured by IL-2 production and also keratinocytes. It strongly and selectively inhibits the classical ( $\alpha$ ,  $\beta$ ) and the novel  $\theta$ -PKC isoforms, with lesser activity for the  $\delta$ -,  $\epsilon$ - and  $\eta$ -PKC isoforms. These PKC isoforms play an important role in signaling pathways downstream of the T cell receptor and the CD28 receptor. Originally developed for the prevention of acute rejection of solid organ allotransplantations, recent studies demonstrated good efficacy in the treatment of psoriasis. In a recently published study, AEB071 was administered orally to 32 patients with severe plaque psoriasis for 2 weeks. There were 4 cohorts of 8 patients each, who received AEB071 in a dose-escalating fashion (ranging from 25 to 300 mg b.i.d.); 2 patients per group received placebo. There was a dose-dependent improvement, showing a PASI 75 for 69% of the treatment group receiving 300 mg b.i.d. [17]. Larger patient cohorts and longer treatment periods will provide further information about the potential of AEB071 as a psoriasis therapy.

### **Selective Modulation/Inhibition of the Immune/Inflammatory Response**

The most commonly used immunosuppressive drugs like cyclosporine and corticosteroids are directed against a myriad of targets involved in the pathogenesis of psoriasis, resulting in a high efficiency but with several adverse effects. Generating more selective therapies might have advantages over classic therapies.

### *Inhibition of T Cell Activation/Elimination of Activated T Cells*

The first hints that T cells are critically involved in the pathogenesis of psoriasis occurred in the mid-1980s, when cyclosporine dramatically cleared psoriatic plaques in clinical trials [18]. Calcineurin inhibitors such as cyclosporine downregulate gene expression in type-1 T cells, Th17 cells and TIP-DC (TNF- and inducible nitric oxide synthase-producing dendritic cells) [19] and show very good efficacy, but side effects (nephrotoxicity, elevation of blood pressure) restrict their long term use. ISA 247 (Voclosporin; Isotechinka, Edmonton, Alta. Canada) has a modification of the functional group at the amino acid 1 residue, and is said to be less nephrotoxic. In a placebo-controlled 4-arm phase III study, 47% of the group receiving the highest dose (0.4 mg/kg b.i.d.) reached a PASI 75 score after 12 weeks, as compared to 4% of the placebo group; 7 out of 113 patients in this group showed mild-to-moderate glomerular filtration rate reductions. Response and side effects were dose-dependent. In comparison to cyclosporine, it seems to have a better outcome concerning changes in renal function [20]. In the early 1990s, there were the first trials testing T-cell-specific