Novel approaches for the treatment of psoriasis

Daniel DiSepio, Roshantha A.S. Chandraratna and Sunil Nagpal

Psoriasis is a common skin disease affecting ~2% of the population. For those who contract the disease it is usually recurrent and sometimes very debilitating. The cause of psoriasis is unknown, although it appears to be an autoimmune disease with a likelihood for genetic predisposition. Past topical treatments such as emollients, coal tar and dithranol have been messy, cosmetically unacceptable and of low efficacy, while systemic therapies such as methotrexate, cyclosporin and acitretin have suffered from significant side effects. New therapies based on medicinal chemistry and an increased understanding of psoriasis have brought us closer to the goal of safe and efficacious treatment of the disease. The authors review some of these new topical and systemic therapies currently in use or in development.

Psoriasis is a recurrent inflammatory skin disorder affecting ~2% of the population. Annually, 1.5 million patients in the USA are seen by physicians for psoriasis with the associated outpatient health care costs estimated to be between $1.6–3.2 billion[1]. According to the National Psoriasis Foundation, there are 150,000–260,000 new cases reported each year with the median age of onset being 28 years (see the National Psoriasis Foundation Web site, http://www.psoriasis.org). In addition, ~5–10% of patients will develop psoriatic arthritis, with inflammation and swelling in the hands, feet and large joints.

The pathogenesis of psoriasis is varied, with a range of morbidity from mild to severe. Each year, ~400 people die from psoriasis-related causes. There are five recognized forms of psoriasis: plaque (also called psoriasis vulgaris), guttate, inverse, erythrodermic and pustular. A patient might exhibit one or more of the forms at the same time and the disease can shift from predominantly one form to another. While the appearance can vary, each form is characterized by epidermal keratinocyte hyperproliferation, abnormal keratinocyte differentiation and immune-cell infiltration. The commonest and most studied form is plaque psoriasis. At the molecular and histological level, plaque psoriasis is characterized by marked keratinocyte hyperproliferation with rete pegs. There is a loss of the granular layer with the accompanying loss of loricrin and filaggrin expression[2,3]. There is overexpression of other differentiation markers such as involucrin, and TGase I, as well as expression of genes such as migration inhibitory factor related protein-8 (MRP-8) and skin-derived antileukoproteinase (SKALP) not found in normal epidermis[3–7]. The expression of the normal suprabasal keratins K1 and K10 are inhibited and replaced by the expression of the hyperproliferative keratins K6 and K16 (Refs 8,9). Related to this hyperproliferation, there is an increased expression of the interleukin 8 (IL-8) receptor[10], cytokines IL-1, IL-6 and IL-8 (Refs 10–12), the epidermal growth factor receptor (EGF-R)[13] and its ligands, transforming growth factor α (TGF-α) and amphiregulin[14,15]. There is a large T-cell infiltration in the affected regions of the skin, with $CD4^+$ lymphocytes in the dermis and $CD8^+$ lymphocytes in the epidermis. These lymphocytes secrete the cytokines IL-2, interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α), which alter keratinocyte proliferation and differentiation[16].

To date, there is still no firm understanding of what causes psoriasis. There are several lines of evidence suggesting that it has at its roots both an autoimmune and a

Daniel DiSepio, **Roshantha A.S. Chandraratna** and **Sunil Nagpal***, Retinoid Research, Departments of Biology and Chemistry, Allergan Inc., Irvine, CA 92623, USA. *tel: +1 714 246 4518, fax: +1 714 246 5578, e-mail: nagpal_sunil@allergan.com

 1359-6446/99/$ – see front matter PII: S1359-6446(99)01335-5

genetic component. Data for both arguments have their merit, and a full disclosure of this information is beyond the scope of this review. Arguments for a genetic predisposition include a third of psoriasis patients having at least one afflicted family member and a 65% concordance for psoriasis in monozygotic twins[17]. In addition, there is an association of the psoriatic phenotype with the HLA antigens HLA-Cw6 and HLA-DR7 (Ref. 17). These data would suggest that a defect resides in the keratinocyte, which, when triggered (potentially by wounding or abrasion), causes the release of cytokines responsible for the recruitment of inflammatory cells. However, there is ample evidence suggesting that psoriasis is caused by a defect in the immune system. There is the presence of $CD4^+$ and $CD8^+$ lymphocytes in psoriatic lesions. T cells isolated from lesions are clonal[18], of the T helper 1 (Th1)-type cytokine subset, and release growth factors and cytokines that cause keratinocyte hyperproliferation. In addition, there is evidence suggesting a role for bacterial superantigens in the pathogenesis of the disease[19]. Of significance is the fact that therapies aimed at suppressing the immune system or anti-inflammatory agents targeting T cells or their derived growth factors are effective in treating the disease. This review will cover the newer topical and systemic treatments for psoriasis and discuss the emerging immunomodulatory agents and cell proliferation inhibitors currently in clinical trials.

Vitamin D_3 analogs

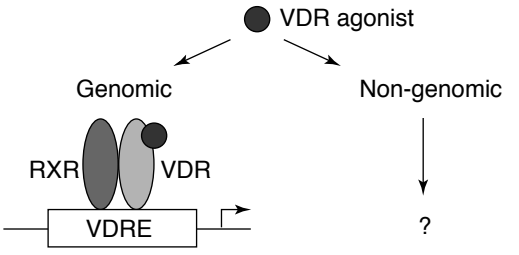
1,25 Dihydroxyvitamin D_3, also called calcitriol, is the biologically active form of vitamin D_3. It exerts its biological activity through the nuclear vitamin D_3 receptor (VDR), which is a member of the steroid hormone receptor superfamily, and through non-nuclear signaling mechanisms that are as yet ill defined. Vitamin D was initially used in high doses orally to treat psoriasis in the 1930s with the assumption that it was the metabolite that helped clear psoriasis after exposure to sunlight. The treatment lost favor, however, owing to a lack of efficacy and hypercalcemic side effects. Subsequent observations demonstrating that keratinocytes and dermal fibroblasts contain vitamin D_3 nuclear receptors[20], and that calcitriol inhibits keratinocyte proliferation and induces differentiation[21], renewed interest in the use of vitamin D_3 for psoriasis. Then there was the observation in a patient showing improvement in psoriasis during a clinical trial using 1α(OH)-D_3 for the treatment of osteoporosis[22]. Promising results were obtained in two subsequent studies using oral 1α(OH)-D_3 (1 mg day^{-1}) in seven patients (complete remission in four patients)[23] and topical treatment with calcitriol in 19 patients (84% clearance or marked improvement)[24].

Two recent studies by Perez *et al.*[25,26] demonstrated that calcitriol is an effective and relatively safe treatment for plaque psoriasis. Improvement was seen in 96% of patients ($n = 84$) treated topically for ten weeks, and 91% showed improvement in a continued long-term 12-month follow up study ($n = 22$)[26]. The drug showed little topical irritation and no statistically significant difference in urinary or serum calcium levels was observed. Similarly, 88% of patients ($n = 85$) showed improvement using oral calcitriol 0.5–3.0 μg day^{-1} over a period of up to three years[25]. By contrast with the topical treatment, oral calcitriol in this study caused a 148% increase in urinary calcium excretion and an increase in serum calcium concentrations, although both were considered to be within the normal range for most patients. Interestingly, in a 1990 pilot study with ten patients suffering from psoriatic arthritis, seven showed statistically significant improvement in their tender joint count[27].

VDR agonists

Medicinal chemists have tried to modify the structure of calcitriol to develop a VDR agonist that exhibits decreased hypercalcemic activity. Several such analogs now exist, including calcipotriol, tacalcitol and KH1060. The most widely used of such analogs is calcipotriol (MC903, calcipotriene, Dovonex), which has been modified to be metabolized very quickly in systemic circulation and is, therefore, 100–200 times less potent than calcitriol in hypercalcemic activity[28]. In comparative clinical trials, the efficacy of topical calcipotriol ointment was generally better compared with two potent topical steroids, betamethasone 17-valerate and fluocinomide (Lidex)[28–30]. In clinical studies using twice-daily treatment, significant improvement was noted in most patients (50–70%), with 10–26% showing complete clearing. A side effect reported with calcipotriol use is topical irritation. This generally occurs in ~20% of patients, but it is usually well tolerated and patient drop-out rates are only 2–3% (Ref. 31). Even though calcipotriol is modified to reduce systemic side effects, there are reported side effects including increases in serum and urinary calcium levels if large amounts of the drug (200 g $week^{-1}$) are used to treat extensive disease[32,33]. Tacalcitol (1α,24 dihydroxyvitamin D_3) is a high-affinity VDR ligand that is very effective in inhibiting keratinocyte proliferation and promoting differentiation, exhibits low hypercalcemic side effects, and appears to be better tolerated than calcipotriol, with only 1% of patients showing irritation as compared with the 20% reported for calcipotriol[34–36].

The exact mechanism of VDR agonist action in inhibiting the psoriatic phenotype remains unclear. Vitamin D_3 and



Cellular effect	Activated genes	Inhibited genes
Anti-proliferation	p21	EGF-R, c-myc
Anti-inflammation	IL-10R	IL-2, IL-6, IL-8, TNF-α, IFN-γ, GM-CSF

Figure 1. *Molecular mechanisms of vitamin D_3 receptor (VDR) agonist action in psoriasis. The VDR forms a heterodimer with the retinoid X receptor (RXR); agonist binding to the VDR moiety of the RXR–VDR heterodimer results in either activation or inhibition of expression of vitamin D_3 responsive genes in skin. EGF-R, epidermal growth factor receptor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN-γ, interferon γ; IL, interleukin; IL-10R, interleukin-10 receptor; TNF-α, tumor necrosis factor α; VDRE, vitamin D_3 response elements.*

its synthetic analogs modulate gene expression through nuclear and non-nuclear mechanisms. Moreover, it is highly doubtful that the regulation of a single gene can account for the effects related to the hormone; rather, it is most likely the regulation of many genes whose concerted action account for the suppression of psoriasis seen in patients. Many of the biological effects of vitamin D_3 and its analogs occur through the VDR, a ligand-dependent transcription factor belonging to the steroid hormone receptor superfamily[37]. VDR can form homodimers or heterodimers with the retinoid X receptor (RXR), which then bind to vitamin D_3 response elements (VDRE) present in the promoters of responsive genes[38] (Fig. 1). With the exception of *$p21^{Waf1,Cip1}$*, most of the genes known to contain VDREs are involved in calcium metabolism and have no known role in psoriasis. However, *$p21^{Waf1,Cip1}$* has been shown to play a role in keratinocyte differentiation[39] and is induced by vitamin D_3 through a VDRE in the p21 promoter[40] (Fig. 1).

Vitamin D_3 inhibits the expression of IL-2, IL-8, IL-6 (in cultured keratinocytes as well as in patients), TNF-α, IFN-γ, EGF-R, MYC (also known as c-myc) and granulocyte–macrophage colony-stimulating factor (GM-CSF) (Fig. 1), all of which play a role in inflammation and proliferation of keratinocytes and T cells[41–46]. Many of these genes are negatively regulated through VDR by ligand-dependent inhibition of AP-1/NF-AT activity[41,44,45,47], while GMCSF is inhibited through a direct binding of a VDR monomer to a region of the gene's promoter[46]. VDR agonists have also been shown to increase the expression of the receptor for the anti-inflammatory cytokine IL-10 (Ref. 48; Fig. 1). Modulation of these genes could account for some of the therapeutics effects seen with vitamin D_3 and its analogs.

Interestingly, in addition to the nuclear signaling mechanisms, vitamin D_3 seems to exert some biological effects by signaling from the cell membrane as well. For example, cycloheximide resistant-increases in intracellular calcium levels occur in keratinocytes within 90 s of calcitriol treatment[49]. This results from inositol triphosphate activation, release of intracellular calcium stores and the opening of cation channels, which allow the influx of additional extracellular calcium. Further, calcitriol treatment results in activation of protein kinase C (PKC) pathways at physiological concentrations with an EC_{50} = 16 nM (Ref. 50). Finally, VDR appears to activate the Ras signaling pathway in a ligand-dependent manner by associating with the adaptor proteins Shc and Src (Refs 51,52). This increase in calcium levels and the activation of PKC and the Ras pathways is a plausible mechanism by which vitamin D_3 halts keratinocyte proliferation and promotes differentiation, thereby slowing the hyperproliferation and abnormal differentiation processes associated with psoriasis. Many of the effects, then, are probably the result of inhibition of cytokine expression and the promotion of keratinocyte differentiation.

Vitamin A analogs; agonists, antagonists, anti-AP1 specific

Retinoic acid and its synthetic analogs bind to two families of nuclear hormone receptors, the retinoic acid receptors (RARα, β and γ) and the retinoid X receptors (RXRα, β and γ). Retinoids positively regulate gene transcription by binding to the RAR–RXR heterodimer, which binds directly to a retinoic acid response element (RARE) in the promoter of an activated gene. Retinoids also negatively regulate the transcription of other genes by antagonizing the enhancing action of transcription factors such as AP-1 and NF-IL6 (Refs 53–57).

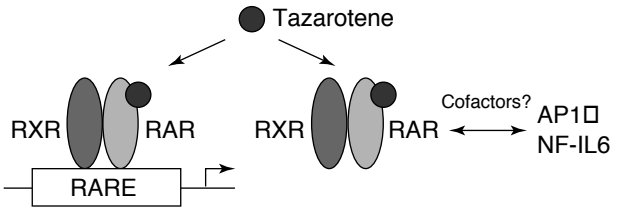
Initial studies in psoriasis using either topical or oral retinoic acid were not very promising because of

unacceptable toxicity and lack of efficacy. Second and third generation aromatic (etretinate and acitretin) and arotinoid (Ro136298 and Ro137410) retinoids were effective orally, but were ineffective topically for the treatment of psoriasis[58,59]. These drugs also had the disadvantage of high levels of toxicity and were contraindicated in women of child-bearing age because of the teratogenicity associated with systemic dosing. Some fourth-generation retinoids, AM80, CD271 (adapalene) and AGN190168 (tazarotene, Tazorac, Zorac), have been shown to be effective treatments topically for plaque psoriasis or acne. Adapalene is used in the clinic for topical treatment of acne but has not been shown to be effective in treating psoriasis, while tazarotene is approved for topical treatment of psoriasis and acne.

Tazarotene

Tazarotene {6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl] nicotinate} is a prodrug of the free acid form, tazarotenic acid, which is specific for the RARs and binds all three receptors, but transactivates selectively through the β/γ subtypes[60]. It is effective in treating mild to moderate plaque psoriasis. In double-blind, multicenter, placebo-controlled studies, 0.05% and 0.1% topical tazarotene gel administered once or twice daily resulted in significant improvement as early as one week[61–63]. Treatment success, defined as >50% improvement or complete clearing, ranged from 63–70%, including the usually difficult knee and elbow lesions. Importantly, the clinical improvement was maintained for 8–12 weeks post-treatment. Recently, a pharmacoeconomic study was conducted comparing the cost effectiveness of fluocinomide, calcipotriene and tazarotene to determine the total cost of achieving a disease-free day. Tazarotene 0.1% was determined to be the most cost-effective, with an expected cost of $49.46 for once daily treatment, compared to $57.74 for tazarotene 0.05%, $91.73 for fluocinomide and $120.56 for calcipotriene[64]. As with other topical retinoids, local irritation is the most common adverse effect, including mild to moderate pruritis, erythema, burning and desquamation[65]. Systemic absorption of tazarotene appears to be very low, leading to no systemic side effects[65].

It has been shown that tazarotene has effects on the three major epidermal manifestations of psoriasis, namely keratinocyte hyperproliferation, abnormal differentiation and immune cell infiltration. Several genes have been identified that are highly or abnormally expressed in psoriatic keratinocytes, including those encoding ornithine decarboxylase (ODC), MRP-8, SKALP, IL-6 and the hyperproliferation keratins K6 and K16. In addition, spinous cell differentiation markers, such as transglutaminase I (TGase I) and involucrin, are overexpressed in psoriasis, while expression of granular cell differentiation markers, such as loricrin and filaggrin, are repressed. This abnormal pattern of gene expression is due to the highly proliferative state of the epidermis caused by the growth factors and cytokines produced by infiltrating immunocytes or activated keratinocytes in the psoriatic skin. Tazarotene inhibits the expression of ODC, TGase I, involucrin, SKALP, MRP-8 and K6 and K16 (Fig. 2), and normalizes the expression of filaggrin in psoriasis as well as in various *in vitro* systems[66–68]. Topical tazarotene has also been shown to inhibit the expression of the adhesion molecules ICAM-1



Cellular effect	Activated RARE genes	Inhibited genes
Normalization of differentiation	TIG1, TIG2	MRP-8, SKALP, TGase I, spr-2, K6, K16
Anti-proliferation	TIG3, p21	ODC, EGF-R
Cell adhesion	Collagen IV	
Anti-inflammation		Stromelysin-1, MRP-8, IL-6

Figure 2. *Molecular mechanisms of tazarotene action in psoriasis. The retinoic acid receptor (RAR) can form a heterodimer with the retinoid X receptor (RXR). Agonist binding to the RAR moiety of the heterodimer results in either induction of expression of RARE-containing genes or inhibition of expression of other genes by antagonism of transcription factors AP-1 or NF-IL6. The antagonism of transcription factors appears to involve competition for limiting co-factors. EGF-R, epidermal growth factor receptor; K6 and K16, hyperproliferative keratins; MRP-8, macrophage migration inhibitory factor related protein 8; ODC, ornithine decarboxylase; SKALP, skin-derived anti-leukoproteinase; spr-2, small proline-rich protein-2; TGase I, transglutaminase I; TIG, tazarotene-induced gene.*

and HLA-DR, both thought to contribute to the psoriatic phenotype by recruiting T cells to the epidermis[67,69]. The inhibition of these genes occurs by either directly antagonizing the effects of transcription factors such as AP-1 and NF-IL6 (Refs 53,57), or indirectly by normalizing the keratinocyte differentiation pathway. In addition to its effects on abnormal differentiation and hyperproliferation, tazarotene also affects the inflammatory response in the skin by antagonizing the action of the proinflammatory proteins TNF-α, IL-2 and IFN-γ (Refs 67,70).

Tazarotene also induces the expression of several novel genes (tazarotene-induced genes, TIGs) in the epidermis and in psoriasis, namely TIG1, -2 and -3 (Fig. 2). Subtractive hybridization was used to identify TIGs 1 and 2 as induced genes in skin-raft cultures treated with tazarotene[71,72]. TIG1 might function as a cell adhesion molecule because it has signature motifs suggesting that it is a transmembrane protein, and it possesses a large extracellular domain with a hyaluronic acid-binding motif. TIG2 has no homology with any known proteins, but contains motifs suggesting that it functions as a soluble or secreted protein. TIG3 was identified by differential display PCR as a gene induced by tazarotene in keratinocyte cultures[73]. The following lines of evidence suggest that TIG3 is a class II tumor suppressor gene[73]:

- It displays significant homology to the previously identified *rev107* tumor suppressor
- It is expressed in a variety of normal tissues but not in cell lines derived from those tissues
- Its expression is reduced in some primary human tumors compared to the adjacent normal tissue
- Forced expression in cell lines reduces their growth rates
- It is localized to chromosome 11q23, a frequently translocated region known to contain several putative tumor suppressors

Given the proposed functions for these three genes, their induction might help to explain some of the antiproliferative effects of tazarotene in psoriasis.

As stated, a major mechanism of action of the retinoic acid receptors is the antagonism of transcription factors AP-1 and NF-IL6. Synthetic retinoids that inhibit the action of these transcription factors, yet fail to transactivate RARs, might serve as effective anti-inflammatory agents with reduced side effects. BMS189453 is a synthetic retinoid that is an antagonist at all three RARs, yet exhibits anti-AP1 activity[74]. Preliminary results have shown that BMS189453 is able to suppress the TPA (12-*O*-tetradecanoylphorbol-13-acetate)-induced expression of IL-8 in monocytes with an EC_{50} of 0.5 μM and to reduce edema and myeloperoxidase activity in inflammatory skin models. These data suggest that anti-AP1 specific retinoids might be useful anti-inflammatory agents with potential use in psoriasis.

Immunosuppressives

Cyclosporin

Cyclosporin is a powerful immunosuppressive originally used in heart, liver and kidney transplant patients. The effects of oral cyclosporin in psoriasis were initially discovered in 1979 (Ref. 75), and subsequently confirmed in several clinical trials. It was these effects that identified the immune system as a key player in the pathogenesis of psoriasis. Cyclosporin acts by inhibiting the action of the transcription factors NF-AT (nuclear factor of activated T cells), AP-3 and NF-κB on the promoter of the gene encoding IL-2 (Ref. 76). These are key transcription factors needed for the early events in antigen-mediated T-cell activation and the production of IL-2. This cyclosporin-mediated block in T-cell activation inhibits the expression of IL-2, IL-4, GM-CSF (granulocyte–macrophage colony-stimulating factor) and IFN-γ (Ref. 77), and probably accounts for the reduced number of $CD4^+$ and $CD8^+$ cells in the epidermis[78]. In addition, it appears that IFN-γ released by intralesional T cells promotes overexpression of psoriatic markers such as HLA-DR, ICAM-1, Cdw60, IP-10 (IFN-γ-inducible protein 10) and MRP-8 in keratinocytes[68,79], and also causes keratinocytes to release cytokines, which serve to activate additional T cells and increase the local inflammation. Cyclosporin, therefore, acts by inhibiting both the activation of T cells and the subsequent activation of keratinocytes by cytokines. Topical cyclosporin is not effective in psoriasis treatment, probably owing to its large size (1202 Da) and lack of bioavailability[80].

Because of the potential side effects associated with long-term systemic cyclosporin use, treatment is usually reserved for severe, widespread or erythrodermic psoriasis, or patients who did not respond to other conventional therapies. Dosage is usually in the 2.5–5 mg kg^{-1} day^{-1} range, with higher doses given initially and then decreased during maintenance until the lowest effective dose is found[80,81]. Most patients achieve remission in their psoriasis [75% reduction in the PASI (psoriasis area and severity index)] within eight weeks of treatment. Limiting side effects, however, include nephrotoxicity, neurological effects and hypertension. These effects tend to be dose and time dependent, and careful monitoring is recommended to keep potential adverse effects to a minimum. Unfortunately, patients tend to relapse very quickly after cessation of treatment. In one recent study, 86% of patients given high-dose cyclosporin (5 mg kg^{-1} day^{-1}) for 16 weeks showed a 70% or more reduction

in involved body surface area[81]. Those that responded to treatment were randomized and entered into a 24-week maintenance phase where they received placebo, 1.5 mg kg^{-1} day^{-1} or 3.0 mg kg^{-1} day^{-1} of cyclosporin. The treatment involving 1.5 mg kg^{-1} day^{-1} did not show much benefit over the placebo group, however, 58% of patients receiving 3.0 mg kg^{-1} day^{-1} controlled their psoriasis for the six-month period of the study. The mechanism of action of immunosuppressive agents is depicted in Fig. 3.

FK506 (tacrolimus, Prograf)

FK506 is an immunosuppressive that is very similar to cyclosporin in its mechanism of action. It blocks the production of IL-2 and T-cell activation by inhibiting the action of the NF-AT transcription factor. Like cyclosporin, it inhibits the activity of a peptidyl-prolyl *cis-trans* isomerase, although the isomerase (FK506 binding protein, FKBP12) is distinct from that inhibited by cyclosporin[82]. Initial clinical results were with four transplant patients with psoriasis and three non-transplant patients with severe psoriasis[83]. All received high doses of FK506 (0.2–0.4 mg kg^{-1} day^{-1}) and all had complete remission within four weeks. Unfortunately, as with cyclosporin treatment, nephrotoxicity and hypertension were observed as side effects. The latest published clinical trial results are from a Phase II double-blind, placebo-controlled study in which patients with severe plaque psoriasis were given oral tacrolimus (n = 27) or placebo (n = 23) for nine weeks[84]. The initial dosage was 0.05 mg kg^{-1} day^{-1}; this was adjusted upwards to 0.1 mg kg^{-1} day^{-1} at the end of three weeks and 0.15 mg kg^{-1} day^{-1} at six weeks if there were no adverse effects. The response rate was 44% for the group treated with tacrolimus at nine weeks, versus 13% for the placebo group, and at these low doses, nephrotoxicity and hypertension were not evident.

Potential topical applications are being evaluated for tacrolimus that, if successful, will provide a great advantage over systemic tacrolimus and cyclosporin treatment. While there are no published results showing topical FK506 efficacy in treating psoriasis, there is ample evidence suggesting that it is readily absorbed through the skin and can suppress local inflammatory reactions. A recent trial testing the effectiveness of topical treatment for atopic dermatitis showed a 67–83% decrease in the summary score for dermatitis in patients receiving 0.03–0.3% tacrolimus ointment over a three-week period[85]. Also, using the Dundee experimental bald rat model of alopecia areata (an auto-inflammatory reaction directed against hair follicles resulting in hair loss), a group recently showed that topical FK506 was effective in reducing follicular infiltration at the site of application[86]. Currently, there are no good treatments for alopecia areata. In this study, all treated rats re-grew hair within 14–21 days, suggesting that topical FK506 could also be useful in treating other human inflammatory diseases.

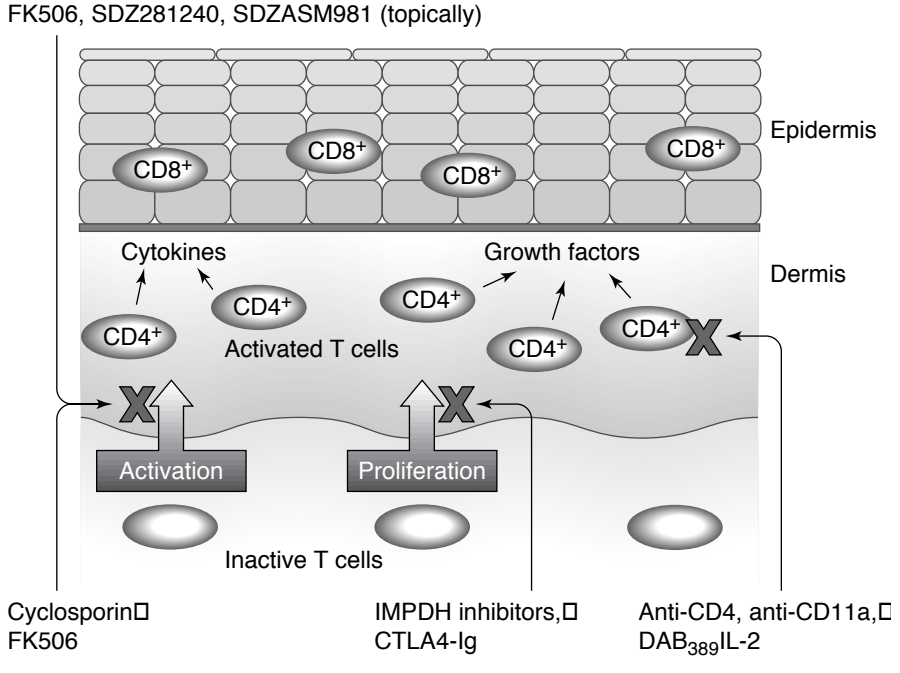


Figure 3. *Mechanisms of action of immunomodulatory compounds in psoriasis. FK506, SDZ281240 and SDZASM981 are topically applied agents and FK506, cyclosporin, inosine-5′-monophosphate dehydrogenase (IMPDH) inhibitors, CTLA4-Ig, anti-CD4, anti-CD11a and* DAB_{389}*IL-2 are systemically administered. These immunosuppressive agents inhibit either the activation or proliferation of inactive T cells, or directly target activated T cells.*

SDZ281240, SDZASM981, A86281

SDZ281240 and SDZASM981 are synthetic derivatives of ascomycin. Both compounds operate through mechanisms similar to FK506, in that they bind to FKBP12 and inhibit the phosphatase activity of calcineurin, resulting in loss of NF-AT activation and, therefore, loss of IL-2 production and T-cell activation[87]. Both drugs have

shown good results in topical dosing for the treatment of allergic contact dermatitis[88], while SDZ281240 has also shown good results in a small clinical study for topical treatment of psoriasis[89]. The study was a randomized, double-blind, placebo-controlled microplaque assay using 1.8 cm Finn Chambers and preparations of SDZ281240, 0.1%, SDZ281240, 0.5%, clobetasol-17-propionate (CP), 0.05% or vehicle. Patient (n = 15) plaques were treated once daily for ten days and evaluations and punch biopsies were taken on day 11. The application of both concentrations of SDZ281240 resulted in reduction of infiltration and erythema, and an almost complete reversion of psoriatic epidermal hyperplasia. Expression of HLA-DR, ICAM-1, ELAM-1/E-selectin, PECAM/CD31 and VCAM-1 was reduced, and there was a reduction of $CD3^+$, $CD4^+$ and $CD8^+$ intraepidermal and dermal lymphocytes.

Using the porcine allergic contact dermatitis model, topical SDZASM981 was as effective as the ultrapotent corticosteroid clobetasol-17-propionate (0.05%) at reducing erythema and infiltration. Preliminary clinical studies in patients with plaque psoriasis showed that topical SDZASM981 (1%) was comparable with clobetasol-17-propionate (0.05%) in reducing psoriasis scores[90]. Like the SDZ compounds, A86281 (ABT281) is a synthetic ascomycin analog. It was synthesized in a search for compounds that are topically effective, but exhibit weak systemic activities following absorption. A86281 and FK506 showed similar topical potency in swine contact hypersensitivity assays, yet A86281 was cleared more rapidly and was less potent when given systemically[91].

IMPDH inhibitors: mycophenolate mofenetil (MMF, CellCept®) and VX497

Inosine-5′-monophosphate dehydrogenase (IMPDH) is a key enzyme in the *de novo* biosynthesis of guanosine nucleotides. Without these nucleotides, B and T cells cannot replicate their DNA. These lymphocytes are especially sensitive to inhibition of IMPDH because they do not have mechanisms to compensate for its loss, whereas other cells have alternate enzyme pathways available. Mycophenolic acid (MPA) is a potent, reversible inhibitor of IMPDH and, therefore, blocks T- and B-cell proliferation. Promising effects of this drug in psoriasis were seen 20 years ago in small studies, in which ~75% of treated patients achieved good to excellent responses[92].

Mycophenolate mofenetil (MMF, CellCept®) is a prodrug of mycophenolic acid, developed and approved for use in renal transplant patients. At least one patient with severe psoriasis treated for five weeks with oral MMF showed a PASI score decrease of 50% (Ref. 93). VX497 is an IMPDH inhibitor that was designed based on data obtained from the X-ray crystal structure of mycophenolic acid bound with its intracellular receptor[94]. VX497 is currently in Phase I/II trials for the oral treatment of psoriasis.

DAB_{389}IL-2

Unactivated T cells express low-affinity IL-2 receptors on their surface comprising β and γ subunits. Upon activation by an antigen, T cells express IL-2 and the α subunit of the receptor. This subunit combines with the β and γ subunits, and the trimer becomes a high-affinity receptor, binding IL-2 and stimulating T-cell growth in an autocrine fashion. The DAB_{389}IL-2 molecule is a fusion protein generated by combining the enzymatic and membrane-translocating domains of the diphtheria toxin with the complete IL-2 protein[95]. This molecule binds to cells containing IL-2 receptors with a 10–1000-fold preference for cells expressing the high-affinity receptor (activated T cells), and is internalized by endocytosis. Once internalized, the enzymatic activity of diphtheria toxin is stimulated, resulting in inhibition of protein synthesis and cell death.

A small pilot study with ten moderate to severe psoriatic patients receiving low doses (2–9 mg kg^{-1} day^{-1}) of DAB_{389}IL-2 showed promising results[96]. Patients were treated intravenously for five consecutive days and the outcome monitored for 23 days. This was repeated at least once for each patient. Eight of ten patients showed some improvement in their PASI scoring, with four showing clearing of some or all of their plaques. The results of a larger, recent trial, however, were less encouraging. This study was designed to study the safety and efficacy in patients receiving higher and more frequent doses of DAB_{389}IL-2 (Ref. 97). Patients received placebo (n = 12), 5 (n = 11), 10 (n = 10) or 15 (n = 8) mg kg^{-1} day^{-1} of DAB_{389}IL-2 for three consecutive days each week, for four consecutive weeks. The outcome was followed for an additional four weeks. The fusion protein was significantly more effective than placebo (p = 0.04), with 41% of patients treated with DAB_{389}IL-2 achieving a 50% or greater improvement in their PASI score, compared with 25% achieving this score for the placebo group. Unfortunately, this would only be considered a moderate effect and this dosing of DAB_{389}IL-2 appeared to have some toxicity. Fever and chills were reported in 76% of patients treated with DAB_{389}IL-2, and two patients experienced treatment-related infections, which were treated with antibiotics. In all, 34% of the patients receiving DAB_{389}IL-2 discontinued treatment owing to adverse events. Although DAB_{389}IL-2 seems to exhibit some anti-psoriatic activity, dosing and treatment schedules must be worked out to achieve the highest efficacy with the least toxicity.

CTLA4-Ig

Antigen-presenting cells (APCs) express a molecule on their surface termed B7, which binds with high affinity to the CTLA4 (CD28) receptor on the T cell to stimulate T-cell proliferation. CTLA4-Ig (BMS188667) is a fusion protein containing the extracellular domain of CTLA4 and the Fc domain of human IgG, which serves to increase serum half-life. This molecule functions as an immunosuppressant by binding to the B7 molecule and blocking the B7–CTLA4 interaction and, thereby, preventing activation of T cells by APCs. Currently, CTLA4-Ig is being developed for transplant rejection and diseases such as rheumatoid arthritis and psoriasis. In a small Phase I safety study involving patients with moderate to severe psoriasis, improvement of 50% or more was seen in five of six patients treated with four doses of 25 mg kg^{-1} per dose and in three of five patients given doses of 4 mg kg^{-1} per dose[98].

Anti-CD4, anti-CD11a and anti-IL-8

Several antibody therapies are currently under development that target key cytokines or cell-surface molecules important for T-cell activation. Because cyclosporin and FK506 act mainly on the activated $CD4^+$ T cells, it was thought that antibodies directed against CD4 would be effective immunosuppressants in psoriasis. Early trials with mouse anti-CD4 monoclonal antibodies were promising, but the antibodies elicited a humoral response against the antibody itself and resulted in $CD4^+$ T-cell depletion[99]. In order to address these issues, a humanized non-depleting monoclonal antibody (mAb) to CD4, OKTcdr4a, was developed from the murine mAb OKT4a. There have been mixed results as to the efficacy of this antibody in treating psoriasis. Initial promising results were obtained in a small clinical trial with six patients: four showed a 50% or greater improvement in their PASI score four weeks after treatment with 1 mg kg^{-1} day^{-1} every other day for a total of three injections[100]. A more recent, slightly larger trial with 28 patients showed less promising results. Patients received a low dose of 225 mg, a high dose of 750 mg or placebo infusions, divided into three infusions over five days. Those who did not respond to the first treatment after five weeks (n = 20) were given a second course. This repeat treatment resulted in a mean decrease in PASI score of 35% two weeks after the second dose[101].

LFA-1 is another cell surface molecule of T cells that is important in activation and adhesion to vascular endothelium and keratinocytes. It is composed of two subunits, CD11a and CD18. Patients with moderate to severe plaque psoriasis (n = 31) were treated with a single low (≤0.3 mg kg^{-1}) or a single high (≥0.6 mg kg^{-1}) dose of humanized mAb (hu1124) directed against CD11a. While PASI scores decreased in both groups (9/16 low group and 13/15 high group), the mean decrease of those who improved was 33%. In addition, mild to severe adverse events were reported, including fever, chills and headache[102].

As stated earlier in this review, IL-8 is an important chemotactic and proinflammatory cytokine in psoriasis. It attracts and activates neutrophils and T cells and acts as a mitogen for keratinocytes. The expression of IL-8 is increased in psoriatic plaques and its receptor is highly expressed on psoriatic keratinocytes. An anti-IL-8 mAb (ABX-IL8) has been produced from a mouse that has been genetically engineered to produce fully human antibodies. This antibody is currently in a Phase I/II multicenter, placebo-controlled trial for treatment of moderate to severe psoriasis (C.G. Davis, pers. commun.).

New therapies on the horizon

In addition to the approaches mentioned above, there are several therapies in preclinical development that might offer additional hope to those suffering from psoriasis. ZK158252 is a leukotriene B_4 (LTB_4) antagonist that inhibits neutrophil infiltration at the site of inflammation. LTB_4 is a chemoattractant and is highly expressed in psoriatic skin, suggesting that it contributes to the pathology of the disease. In guinea pig inflammation models, topical ZK158252 was able to block hyperproliferation, edema and neutrophil infiltration completely after topical administration of LTB_4 or a Ca^{2+}-ionophore[103]. EGF binds to the epidermal growth factor receptor (EGF-R) and transduces a proliferative signal in keratinocytes via a tyrosine kinase cascade. SU5271 is a small synthetic molecule that specifically inhibits the EGF-R tyrosine kinase cascade and might, therefore, inhibit the hyperproliferative phenotype of psoriatic keratinocytes[1]. PKC regulates normal growth and differentiation in keratinocytes and its dysregulation is suspected to be involved in the inflammation and abnormal differentiation observed in psoriasis. SCH47112 is another kinase inhibitor that interacts with the catalytic domain of PKC and has been shown to inhibit TPA-induced inflammation in a hairless mouse model as well as TPA-induced differentiation in cultured human keratinocytes[104]. Other applications include the possible use of the anti-inflammatory cytokines IL-10 and IL-11 (Refs 105,106), as well as T-cell-receptor peptide vaccines currently in Phase II trials.

Conclusions

The efficacy of different types of drug in the treatment of psoriasis and the multifactorial etiology of the disease suggests that psoriasis can be managed therapeutically by

agents that either modulate the immune system or normalize the differentiation program of psoriatic keratinocytes. Calcipotriol and tazarotene are significant additions to the topical anti-psoriatic armamentarium of dermatologists. Because they represent the first generation of topical vitamin D_3- and vitamin A-based drugs, there is room for improvement with newer drugs. In addition, further research into the use of these agents in combination with other therapeutic regimens is required. The former objective can be achieved by the systematic synthesis of the next generation of receptor- or function-selective vitamin D_3, or retinoid-based compounds. For example, in the case of retinoids, the activity through RARγ is desirable because it constitutes >90% of the RAR repertoire in skin. Therefore, RARγ-selective retinoids might show an improved therapeutic index. Alternatively, function-selective retinoids – for example, dissociated retinoids with only anti-AP1 activity or inverse agonists – might exhibit less toxic effects. Recently, tazarotene has been tried in combination with steroids and UVB phototherapy. Tazarotene in combination with mid- or high-potency steroid showed significantly greater efficacy and decreased incidence of adverse effects[107,108]. In combination with phototherapy, tazarotene increased the efficacy of UVB treatment[109]. Therefore, it appears that we need to treat psoriasis with combination regimens in a manner similar to the treatment of other hyperproliferative diseases.

As retinoids, steroids, vitamin D_3 (deltanoids) and immunomodulatory agents affect psoriasis by different mechanisms, a combination of some of these agents has theoretical appeal and such a regimen might exhibit synergistic therapeutic effects. The implementation of modern genomics approaches to the understanding of the pathogenesis of diseased skin is likely to lead to the identification of novel molecular targets and novel therapeutics for the treatment of psoriasis. These approaches have identified MRP-8, SKALP, TIG1, TIG2 and TIG3 as the molecular targets of retinoid action in the psoriatic skin. It remains to be seen whether other small chemical entities affecting the expression of some of these genes would also be useful in the treatment of psoriasis. We believe that an increased understanding of the biology of the lesions, along with the elucidation of the mechanisms of action of various therapeutic agents, is likely to lead us into a new era of psoriasis therapy. For now, the wait for a 'cure' for psoriasis by 2% of the population continues.

REFERENCES

1 Nagpal, S. and Chandraratna, R.A.S. (1997) *Ann. Rep. Med. Chem.* 32, 201–210
2 Hohl, D. (1993) *Am. J. Dermatopathol.* 15, 20–27
3 Bernard, B.A. *et al.* (1988) *J. Invest. Dermatol.* 90, 801–805
4 Schroeder, W.T. *et al.* (1992) *J. Invest. Dermatol.* 99, 27–34
5 Madsen, P. *et al.* (1991) *J. Invest. Dermatol.* 97, 701–712
6 Nonomura, K. *et al.* (1993) *Br. J. Dermatol.* 128, 23–28
7 Schalkwijk, J. *et al.* (1993) *J. Invest. Dermatol.* 100, 390–393
8 Thaler, M. *et al.* (1980) *J. Invest. Dermatol.* 75, 156–158
9 Thewes, M. *et al.* (1991) *Arch. Dermatol. Res.* 283, 465–471
10 Schultz, B.S. *et al.* (1993) *J. Immunol.* 151, 4399–4406
11 Debets, R. *et al.* (1995) *Eur. J. Immunol.* 25, 1624–1630
12 Grossman, R.M. *et al.* (1989) *Proc. Natl. Acad. Sci. U. S. A.* 86, 6367–6371
13 Nanney, L.B. *et al.* (1986) *J. Invest. Dermatol.* 86, 260–265
14 Elder, J.T. *et al.* (1989) *Science* 243, 811–814
15 Cook, P.W. *et al.* (1992) *Cancer Res.* 52, 3224–3227
16 Baadsgaard, O. *et al.* (1990) *J. Invest. Dermatol.* 95, 32S–34S
17 Krueger, G.G. and Duvic, M. (1994) *J. Invest. Dermatol.* 102, 14S–18S
18 Chang, J.C.C. *et al.* (1995) *Ann. New York Acad. Sci.* 756, 370–381
19 Valdimarsson, H. *et al.* (1995) *Immunol. Today* 16, 145–149
20 Feldman, D. *et al.* (1980) *J. Clin. Endocrinol. Metab.* 51, 1463–1465
21 Hosomi, J. *et al.* (1983) *Endocrinology* 113, 1950–1957
22 Morimoto, S. and Kumahara, Y. (1985) *Med. J. Osaka Univ.* 35, 51–54
23 Takamoto, S. *et al.* (1986) *Calcif. Tissue Int.* 39, 360–364
24 Morimoto, S. *et al.* (1986) *Br. J. Dermatol.* 115, 421–429
25 Perez, A. *et al.* (1996) *Br. J. Dermatol.* 134, 1070–1078
26 Perez, A. *et al.* (1996) *Br. J. Dermatol.* 134, 238–246
27 Huckins, D. *et al.* (1990) *Arthritis Rheum.* 33, 1723–1727
28 Kragballe, K. (1995) *Pharmacol. Toxicol.* 77, 241–246
29 Bruce, S. *et al.* (1994) *J. Am. Acad. Dermatol.* 31, 755–759
30 Ramsay, C.A. *et al.* (1994) *Dermatology* 189, 260–264
31 Berth-Jones, J. (1996) *Br. J. Clin. Pract.* 83 (Suppl.), 1–32
32 Dwyer, C. and Chapman, R.S. (1991) *Lancet* 338, 764–765
33 Bourke, J.F *et al.* (1993) *Br. J. Dermatol.* 129, 74–76
34 Matsunaga, T. *et al.* (1990) *J. Dermatol.* 17, 135–142
35 Kato, T. *et al.* (1987) *Br. J. Dermatol.* 117, 528–530
36 Van De Kerkhof, P. *et al.* (1996) *Br. J. Dermatol.* 135, 758–765
37 Baker, A.R. *et al.* (1988) *Proc. Natl. Acad. Sci. U. S. A.* 85, 3294–3298
38 Carlberg, C. *et al.* (1993) *Nature* 361, 657–660
39 Di Cunto, F. *et al.* (1998) *Science* 280, 1069–1072
40 Liu, M. *et al.* (1996) *Genes Dev.* 10, 142–153
41 Muller, K. and Bendtzen, K. (1996) *J. Invest. Dermatol. Symp. Proc.* 1, 68–71
42 Koizumi, H. *et al.* (1997) *J. Dermatol. Sci.* 15, 207–213
43 Kang, S. *et al.* (1998) *Br. J. Dermatol.* 138, 77–83
44 Oxholm, A. *et al.* (1989) *Acta. Derm. Venereol.* 69, 385–390
45 Matsumoto, K. (1990) *Biochem. Biophys. Res. Commun.* 166, 916–923
46 Towers, T.L. and Freedman, L.P. (1998) *J. Biol. Chem.* 273, 10338–10348
47 Tsoukas, C.D. *et al.* (1984) *Science* 224, 1438–1440

48 Michel, G. *et al.* (1997) *Inflamm. Res.* 46, 32–34
49 Bittiner, B. *et al.* (1991) *Br. J. Dermatol.* 124, 230–235
50 Slater, S.J. *et al.* (1995) *J. Biol. Chem.* 270, 6639–6643
51 Gniadecki, R. (1996) *J. Invest. Dermatol.* 106, 1212–1217
52 Gniadecki, R. (1998) *Biochem. Pharmacol.* 55, 499–503
53 Chambon, P. (1994) *Semin. Cell Biol.* 5, 115–125
54 Mangelsdorf, D.J. *et al.* (1994) in *The Retinoids: Biology, Chemistry and Medicine* (Sporn, M.B., Roberts, A.B. and Goodman, D.S., eds), p. 319, Raven Press
55 Nagpal, S. *et al.* (1993) *EMBO J.* 12, 2349–2360
56 Zhang, X.K. *et al.* (1992) *Nature* 358, 587–591
57 DiSepio, D. *et al.* (1997) *J. Biol. Chem.* 272, 25555–25559
58 Orfanos, C.E. *et al.* (1985) *Curr. Probl. Dermatol.* 13, 33–49
59 Orfanos, C.E. *et al.* (1987) *Drugs* 34, 459–503
60 Nagpal, S. *et al.* (1995) *J. Biol. Chem.* 270, 923–927
61 Weinstein, G. *et al.* (1995) *J. Invest. Dermatol.* 104, 661
62 Weinstein, G.D. (1996) *Br. J. Dermatol.* 135 (Suppl. 49), 33–37
63 Krueger, G.G. *et al.* (1998) *Arch. Dermatol.* 134, 57–60
64 Marchetti, A. *et al.* (1998) *Clin. Ther.* 20, 851–869
65 Marks, R. (1996) *Br. J. Dermatol.* 135 (Suppl. 49), 27–32
66 Chandraratna, R.A.S. (1996) *Br. J. Dermatol.* 135 (Suppl. 49), 506–517
67 Esgleyes-Ribot, T. *et al.* (1994) *J. Am. Acad. Dermatol.* 30, 581–590
68 Nagpal, S. *et al.* (1996) *Cell Growth Differ.* 7, 1783–1791
69 Griffiths, C.E.M. *et al.* (1989) *J. Am. Acad. Dermatol.* 20, 617–629
70 Becherel, P.A. *et al.* (1996) *J. Invest. Dermatol.* 106, 1182–1186
71 Nagpal, S. *et al.* (1996) *J. Invest. Dermatol.* 106, 269–274
72 Nagpal, S. *et al.* (1997) *J. Invest. Dermatol.* 109, 91–95
73 DiSepio, D. *et al.* (1998) *Proc. Natl. Acad. Sci. U. S. A.* 95, 14811–14815
74 Hei, Y.J. *et al.* (1998) *FASEB J.* 12, A1464
75 Mueller, W. and Hermann, B. (1979) *New Engl. J. Med.* 301, 555
76 DeFranco, A.L. (1991) *Nature* 352, 754
77 McCaffrey, P.G. *et al.* (1994) *J. Biol. Chem.* 269, 30445–30450
78 Baker, B.S. *et al.* (1987) *Br. J. Dermatol.* 116, 503–510
79 Kadunce, D.P. and Krueger, G.G. (1995) *Dermatol. Clin.* 13, 723–737
80 Herman, R.C. *et al.* (1988) *Skin Pharmacol.* 1, 246–249
81 Shupack, J. *et al.* (1997) *J. Am. Acad. Dermatol.* 36, 423–432
82 McKeon, F. (1991) *Cell* 66, 823–826
83 Jegasothy, B.V. *et al.* (1992) *Arch. Dermatol.* 128, 781–785
84 European FK506 Multicenter Psoriasis Study Group (1996) *Arch. Dermatol.* 132, 419–423
85 Bieber, R.T. *et al.* (1997) *New Engl. J. Med.* 337, 816–821
86 McElwee, K.J. *et al.* (1997) *Br. J. Dermatol.* 137, 491–497
87 Bevec, D. *et al.* (1997) *Australasian J. Dermatol.* 38 (Suppl. 2), 285
88 Van Leent, E.J. *et al.* (1998) *Arch. Dermatol.* 134, 805–809
89 Rappersberger, K. *et al.* (1996) *J. Invest. Dermatol.* 106, 701–710
90 Mrowietz, U. *et al.* (1997) *Australasian J. Dermatol.* 38 (Suppl. 2), 44
91 Mollison, K.W. *et al.* (1997) *J. Invest. Dermatol.* 108, 572
92 Spatz, S. *et al.* (1978) *Br. J. Dermatol.* 98, 429–435
93 Haufs, M.G. *et al.* (1998) *Br. J. Dermatol.* 138, 179–181
94 Sintchak, M.D. *et al.* (1996) *Cell* 85, 921–930
95 vanderSpek, J.C. *et al.* (1993) *J. Biol. Chem.* 268, 12077–12082
96 Gottlieb, S.L. *et al.* (1995) *Nat. Med.* 1, 442–447
97 Bagel, J. *et al.* (1998) *J. Am. Acad. Dermatol.* 38, 938–944
98 Lebwohl, M. *et al.* (1997) *J. Invest. Dermatol.* 108, 570
99 Morel, P. *et al.* (1992) *J. Autoimmun.* 5, 465–477
100 Bachelez, H. *et al.* (1998) *J. Autoimmun.* 11, 53–62
101 Gottlieb, A.B. *et al.* (1998) *J. Invest. Dermatol.* 110, 687
102 Gottlieb, A.B. *et al.* (1998) *J. Invest. Dermatol.* 110, 679
103 Levitzki, A. and Gazit, A. (1995) *Science* 267, 1782–1788
104 Reynolds, N.J. *et al.* (1997) *Arch. Dermatol. Res.* 289, 540–546
105 Asadullah, K. *et al.* (1998) *J. Clin. Invest.* 101, 783–794
106 Trepicchio, W.L. *et al.* (1996) *J. Immunol.* 157, 3627–3634
107 Lebwohl, M. and Poulin, Y. (1998) *J. Am. Acad. Dermatol.* 39, S139–S143
108 Lebwohl, M.G. *et al.* (1998) *J. Am. Acad. Dermatol.* 39, 590–596
109 Koo, J.Y. (1998) *J. Am. Acad. Dermatol.* 39, S144–S148