BP-1107 [{2-[4-(2,4-Dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide]: A Novel Synthetic Thiazolidinedione That Inhibits Epidermal Hyperplasia in Psoriatic Skin-Severe-Combined Immunodeficient Mouse Transplants after Topical Application

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ABSTRACT

Recent studies have demonstrated that orally administered thiazolidinedione ligands of the peroxisome proliferator-activated receptor-γ can ameliorate clinical features of psoriasis in humans. Thiazolidinediones also inhibit the proliferation of psoriatic keratinocytes in monolayer and organ culture, and at least one of these agents (troglitazone) inhibits epidermal hyperplasia of human psoriatic skin transplanted to severe-combined immunodeficient (SCID) mice. In the present study, we show that a novel, synthetic, thiazolidinedione derivative, BP-1107 ({2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide), is capable of inhibiting psoriatic hyperplasia in the SCID mouse transplant model after topical application. Like other thiazolidinediones, BP-1107 inhibits proliferation of rapidly growing keratinocytes in monolayer culture, but compared with these agents, the effective dose of BP-1107 needed to suppress keratinocyte proliferation is much lower. Concentrations of BP-1107 that effectively inhibit keratinocyte function have no detrimental effect on dermal fibroblasts. These data suggest that effective topical antipsoriatic therapy may be provided with this agent.

Psoriasis is an inflammatory skin disease characterized by excessive keratinocyte proliferation, leading to a significant thickening of the epidermis, expansion of epidermal rete pegs into papillary dermal space, and continuous shedding of the thickened epidermis. The etiology of the disease is complex and not well understood. T cells are almost certainly involved in the initiation of psoriatic lesions. Activated T cells in the region of the dermal-epidermal junction are thought to drive the hyperplastic proliferative response through elaboration of Th1 cytokines, including tumor necrosis factor-α, interferon-γ, and various interleukins (IL-2, IL-6, and IL-8) (Nickoloff, 1991; Valdimarsson et al., 1995; Austin et al., 1999). Although the immune system is likely to be responsible for initiating the disease, the subsequent hyperproliferative response in the keratinocytes seems to be a direct consequence of proproliferative intraepidermal events. In recent studies, we (Ellis et al., 2000; Bhagavathula et al., 2004) and other investigators (Komuves et al., 1998; Kubota et al., 1998; Mueller et al., 1998; Rivier et al., 1998, This study was supported in part by Grants R41 AR44767 and R41 AR50330 from the National Institutes of Health. H.A.P. and T.W.K. have equity in Bethesda Pharmaceuticals, Inc. and could have financial gain if the drug under study proves to be effective. Article, publication date, and citation information can be found at http://jpet.aspetjournals.org. doi:10.1124/jpet.105.091066.

ABBREVIATIONS: Th, T-helper; IL, interleukin; PPAR-γ, peroxisome proliferator-activated receptor-γ; SCID, severe-combined immunodeficient; BP-1107, {2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide; ERK, extracellular signal-regulated kinase; MMP, matrix metalloproteinase; EGF, epidermal growth factor; DMSO, dimethyl sulfoxide; KGM, keratinocyte growth medium; KBM, keratinocyte basal medium; PAGE, polyacrylamide gel electrophoresis.
200; Sarraf et al., 1998; Mao-Qiang et al., 2004) have shown that agonists of the peroxisome proliferator-activated receptor-γ (PPAR-γ), including thiazolidinediones such as troglitazone, rosiglitazone, and pioglitazone, reduce epithelial cell proliferation and induce differentiation. At least one of the thiazolidinediones (i.e., troglitazone) normalizes the histological appearance of human psoriatic skin in organ culture and in the human skin-severe-combined immunodeficient (SCID) mouse model (Ellis et al., 2000). Both troglitazone and pioglitazone have been shown to reduce the clinical and histological presentation of psoriasis after systemic treatment (Pershadsingh et al., 1998; Ellis et al., 2000; Robertshaw and Friedman, 2005; Shafiq et al., 2005). Unfortunately, these agents cause serious side effects (fluid retention and weight gain) in a subset of patients. Although the first clinically approved thiazolidinedione ligand of PPAR-γ (troglitazone) was withdrawn from the market because of hepatotoxicity, this does not seem to be a class effect because liver toxicity has not been an issue with other PPAR-γ activators such as pioglitazone or rosiglitazone (Lebovitz, 2002).

Recently, we synthesized a series of thiazolidinedione PPAR-γ agonists. One of these agents (referred to as BP-1107) was shown to have high affinity for PPAR-γ (EC_{50} of 26 pM compared with 64 nM for rosiglitazone) (Bhagavathula et al., 2004). Given the high affinity of BP-1107 for PPAR-γ, we conducted a series of experiments to assess the ability of this agent to modulate keratinocyte proliferation in vitro and epidermal thickness in the human skin-SCID mouse transplant model. Our results show that BP-1107 is a potent keratinocyte growth inhibitor in vitro and effectively reduces epidermal hyperplasia of human psoriatic skin transplanted to SCID mice. Of significance, BP-1107 is effective when delivered topically.

Materials and Methods

BP-1107. BP-1107, a novel high-affinity PPAR-γ ligand, was obtained from Dr. Avery (Department of Medicinal Chemistry, University of Mississippi, Oxford, MS) and Bethesda Pharmaceuticals, Inc. (Bakersfield, CA). Structurally, BP-1107 is an adamantyl-coupled thiazolidinedione (Fig. 1).

Other Reagents. Commercial reagents used in this study included antibodies to phospho-ERK1/2, total-ERK1/2, phospho-c-Jun, thiazolidinedione (Fig. 1). Hematoxylin and eosin, skin sections were examined by light microscopy. Tissue sections were visualized by light microscopy at 200× magnification. Epidermal thickness measurements were made at four or more sites on three or four different histological sections from each transplant (two control and two BP-1107-treated biopsies per subject) and averaged. From these values, mean epidermal thickness was determined.

Human Epidermal Keratinocytes and Dermal Fibroblasts in Monolayer Culture. Normal human epidermal keratinocytes were isolated as described previously (Varani et al., 1994). Primary and early passage cells were maintained in keratinocyte growth medium (KGM) (Cambrex Bio Science Walskeville, Walskeville, MD). KGM is a modification of MCDB-153 medium containing a low level (0.15 mM) of extracellular Ca^{2+} and further supplemented with a mixture of growth factors, including 0.1 ng/ml EGF, 0.5 μg/ml insulin, and 2% bovine pituitary extract. Fibroblasts were obtained from the same tissue and grown in monolayer culture using Dulbeco's modified Eagle's medium supplemented with nonessential amino acids and 10% fetal bovine serum. Both keratinocytes and fibroblasts were maintained at 37°C in an atmosphere of 95% air and 5% CO_{2}. Cells were subcultured by exposure to EDTA and used at passage 2 to 3.

Proliferation Assays. For dose-response studies, keratinocytes and fibroblasts were seeded at 5 × 10^{4} cells/well in their respective growth media (24-well plate) and allowed to attach overnight. Cells were treated with different concentrations of BP-1107. Proliferation was measured on day 3 by releasing the cells with trypsin/EDTA and enumerating them using a particle counter (Beckman Coulter, Inc., Fullerton, CA). For time-course studies, 5 × 10^{5} cells were seeded per well in a 24-well plate, allowed to attach overnight, and treated with 1 μM BP-1107. Cell counts were made on days 1 through 3. KGM was used for keratinocyte proliferation studies, and KGM supplemented with 1.4 mM Ca^{2+} was used for fibroblast proliferation assays. KGM consists of the same basal medium as KGM but is not supplemented with growth factors.

Cytotoxicity Assays. Keratinocytes were plated at 5 × 10^{4} cells/well in KGM and incubated overnight to allow the cells to attach. On the next day, cells were exposed to control conditions or to different concentrations of BP-1107 for 4 h. At the end of the incubation period, the cells were harvested, counted, and replated in growth medium. Eighteen hours later, the percentage of cells that had reattached and spread was determined. The ability of cells to reattach and spread after treatment was used as a measure of cell viability (Varani et al., 1985).

Motility Assay. Motility was assessed using the “scratch wound” assay. The cells were seeded into a 24-well dish at 1 × 10^{6} cells/well and incubated in KGM to near confluence. At that point, a scratch-wound approximately 100 μm in width was made through the mono-
layer. The wounded monolayers were incubated in KGM with different concentrations of BP-1107 for 2 days. At the end of the incubation period, the cultures were photographed under phase-contrast microscopy at 200× magnification. The distance the cells migrated into the wounded area was measured using a micrometer.

**MMP Assays.** Keratinocyte- or fibroblast-conditioned medium was assayed for MMP activity. SDS-PAGE substrate embedded enzymography (zymography) was used to identify enzymes with gelatinase activity. Assays were carried out as described in a previous report (Gibbs et al., 1999). In brief, denatured but unreduced culture fluid samples were resolved in 10% SDS-PAGE gels prepared with incorporation of gelatin (1 mg/ml) before casting. After electrophoresis, gels were washed twice for 15 min in 50 mM Tris buffer containing 1 mM Ca²⁺, 0.5 mM Zn²⁺, and 2.5% Triton X-100. The gels were then incubated overnight in Tris buffer with 1% Triton X-100 and stained the next day with Brilliant Blue 250-R. After destaining, zones of enzyme activity were detected as regions of negative staining against the dark background. Gelatin zymography is used for detection of MMP-2 (72-kDa gelatinase A) and MMP-9 (92-kDa gelatinase B).

Fibroblast-conditioned medium was assayed for MMP-1 (interstitial collag enase) by Western blotting as described previously (Bhagavathula et al., 2004). In brief, samples were separated in 10% SDS-PAGE under denaturing and reducing conditions and transferred to nitrocellulose membranes. After blocking with a 5% nonfat milk solution in Tris-buffered saline at 4°C overnight, membranes were incubated for 1 h at room temperature with a rabbit polyclonal anti-human MMP-1 antibody, diluted 1:6000 in 0.5% nonfat milk/0.1% Tween 20-Tris-buffered saline. Thereafter the membranes were washed with 0.1% Tween 20-Tris-buffered saline and bound antibody detected using the phototope-HRP Western blot detection kit (Cell Signaling Technology Inc.).

**Type I Procollagen Assay.** Fibroblast-conditioned medium was assayed for type I procollagen by enzyme-linked immunosorbent assay (Pan Vera Corp., Madison, WI) as described previously (Varani et al., 2000). The procollagen assay uses an antibody to the C-terminal propeptide region that is part of the collagen molecule as it is synthesized and secreted (before being proteolytically cleaved). As such, this assay is a measure of newly synthesized collagen.

**Preparation of Cell Lysates and Immunoblot Analysis of Signaling Intermediates.** Cells were lysed in 1× cell lysis buffer (Cell Signaling Technology Inc.). Lysis was performed at 4°C by scraping the cells into lysis buffer and sonicating the samples. Cell lysates were incubated on ice for 30 min and then cleared by microcentrifugation at 16,000g for 15 min. The supernatant fluids were collected and protein concentration was estimated using the Bio-Rad DC protein assay kit (Bio-Rad, Hercules, CA). Cell extracts containing equivalent amounts of protein (40 μg of total protein per lane) were electrophoresed in 10% SDS-polyacrylamide gels. Western blotting for signaling intermediates was carried out as described above for MMP-1.

**Statistical Analysis.** Measurements were expressed as means ± S.E. or means ± S.D. Statistical analyses were carried out using the Student’s t test where two groups were compared or by analysis of variance followed by paired group comparisons where there were multiple groups. p < 0.05 was considered statistically significant.

**Results**

**Effects of Topical Treatment of Human Skin-SCID Mouse Transplants with BP-1107.** In the first series of experiments, psoriatic lesional skin from two individuals was transplanted to SCID mice (four animals per subject). After allowing the skin to heal, two animals from each group were treated topically with BP-1107 (100 μl of a 100 μM solution dispensed over the treatment area with a micropipette on 21 consecutive days), whereas the other two received vehicle alone. At the end of the treatment period, skin sites were photographed. Grossly, the human tissue treated with BP-1107 became visibly thinned (compared with skin from animals treated with vehicle alone). In places, the epidermis seemed to be completely eroded. In other areas, the treated tissue shrank such that the area covered by the transplant decreased. Figure 2, top, demonstrates the gross features of control and BP-1107-treated psoriatic skin transplants.

Figure 2, middle, demonstrates histological features of skin from vehicle-treated and BP-1107-treated mice. The vehicle-treated skin had the typical features of psoriatic plaque skin, including thickened epidermis with associated rete ridges and pegs, along with inflammatory foci and with focal loss of the granular layer (Fig. 2C). In contrast, the epidermis from animals treated with BP-1107 was much thinner than skin from the untreated animals. There was no evidence of rete pegs or ridges (Fig. 2D). Figure 2, bottom, provides quantitative information based on epidermal thickness measurements. Overall, the epidermal thickness of skin from BP-1107-treated animals was thinned, compared with skin from untreated mice.

In addition to transplanting and treating psoriatic plaque skin, skin from four nonpsoriatic donors was also transplanted to SCID mice and treated topically with BP-1107. With nonpsoriatic skin samples, BP-1107 was used at two concentrations (25 and 100 μM). Consistent with past reports (Zeigler et al., 2001; Bhagavathula et al., 2005), skin from nonpsoriatic tissue donors became hyperplastic upon transplantation. When the nonpsoriatic skin transplants were treated topically with a 100 μM concentration, findings were similar to those with psoriatic skin, i.e., shrinkage of the tissue and areas of epidermal erosion were observed. These gross changes were not observed in animals treated with the lower concentration. Histological findings including thinning of the epidermis with loss of rete pegs and ridges were observed with both drug concentrations (Fig. 3).

**Effects of BP-1107 on Keratinocyte Function in Monolayer Culture.** Human epidermal keratinocytes were treated with BP-1107 in monolayer culture and effects on proliferation, motility, and elaboration of MMP-9 assessed. As shown in Fig. 4, keratinocyte proliferation was inhibited by BP-1107 in a dose- and time-dependent manner. Significant inhibition of growth was achieved at a concentration of 0.5 μM (ED₅₀ = 0.65 μM). Growth inhibition did not seem to reflect cytotoxicity, because there was no evidence of cell death in the 4-h cytotoxicity assay with drug concentrations between 0.1 and 2 μM. Additionally, studies were carried out in which keratinocytes were treated with concentrations of BP-1107 between 0.1 and 2 μM for a 2-day period. At the end of the treatment period, the cells were washed. Half was reincubated in medium with the same concentrations of BP-1107, and the other half was incubated in control growth
medium. After two additional days of incubation, cells were harvested and counted. As shown in Fig. 5, growth inhibition with BP-1107 was fully reversible. That is, cells that were treated with BP-1107 for 2 days and then incubated in drug-free medium grew as rapidly between days 2 and 4 as cells not exposed to drug initially.

In contrast to these results, exposure of cells to higher concentrations of BP-1107 (10–20 μM) was cytotoxic. Specifically, the number of cells recovered from wells at the end of the 3-day incubation period was fewer than the number plated (indicative of cell killing) and this was verified by cell death in the 4-h cytotoxicity assay (not shown).

Keratinocyte motility was assessed next. As shown in Fig. 6, cell migration was inhibited in the presence of BP-1107. The dose-response for inhibition of motility (ED_{50} = 0.55 μM) was slightly lower than that for proliferation.

Supernatant fluids were collected from untreated and BP-1107-treated keratinocytes and assayed for MMP-2 and MMP-9 by gelatin zymography. Results from this study indicated no significant effect on either enzyme (not shown).

**Effects of BP-1107 on Intracellular Signaling Events That Underlie Proliferation, Motility, and MMP Production in Keratinocytes.** Previous studies have demonstrated the importance of mitogen-activated protein kinase signaling (in particular, signaling through the ERK1/2 pathway) to EGF-induced biological events in keratinocytes (Zeigler et al., 1999). To determine whether the inhibitory effects of BP-1107 on keratinocyte function could be related to interference with mitogen-activated protein kinase signaling, we assessed the effects of the synthetic PPAR-γ agonist on ERK1/2 phosphorylation in EGF-stimulated keratinocytes. For this experiment, keratinocytes were treated with 10 ng/ml EGF in the absence or presence of BP-1107. At various times later, ERK1/2 phosphorylation was assessed. Inhibition was seen as early as 5 min after EGF stimulation, was maximal at 15 min, and gradually returned to baseline by 120 min (Fig. 7). In addition to the rapid/transient reduction in the phosphorylation of both ERK1 and ERK2, there was also a longer sustained reduction. This was observed by assessing phospho-ERK1/2 levels in control and BP-1107-
treated keratinocytes after 1 and 2 days of treatment. On both days, the levels of phospho-ERK1/2 were lower in treated than control cells (Fig. 7). In contrast to effects on phospho-ERK1/2, there was no measurable effect of BP-1107 treatment on total ERK1/2 levels in either the short-term (5- to 120-min) or long-term (1- and 2-day) studies.

In a final set of experiments, we examined the ability of BP-1107 to reduce c-Jun phosphorylation in keratinocytes. In contrast to what was observed with ERK1/2, treatment with BP-1107 produced essentially no change in the amount of phosphorylated c-Jun seen in keratinocytes over a 6-h time period after EGF stimulation (not shown). Likewise, there was no change in total c-Jun expression. The lack of effect on c-Jun is of interest since there was no change in MMP-9 expression under the same conditions. Previous studies have shown a role of c-Jun in MMP-9 induction (Fisher et al., 1998).

**Effects of BP-1107 on Fibroblast Function in Monolayer Culture.** In addition to assessing BP-1107 on keratinocyte function, human dermal fibroblasts isolated from the same skin samples as the keratinocytes were also examined for response to BP-1107. Fibroblast proliferation and procollagen synthesis proved to be resistant to the effects of this agent. When treated with a concentration of 1 μM, there was no significant effect on fibroblast proliferation over the 3-day observation period (Fig. 8, top). Likewise, there was no inhibition of type I procollagen elaboration under the same conditions (Fig. 8, middle). On the other hand, fibroblast production of MMP-1 (interstitial collagenase), which is the major collagen-degrading enzyme in human skin (Brennan et al., 2003), was reduced in the presence of BP-1107 (Fig. 8, bottom).

**Discussion**

Thiazolidinediones such as troglitazone, rosiglitazone, and pioglitazone were originally developed for use in the treatment of type II diabetes, but it was observed early on that, when individuals with psoriatic plaques were treated with troglitazone, there was an improvement in their psoriasis (Pershadsingh et al., 1998; Ellis et al., 2000). Subsequently, it was demonstrated in controlled studies that these synthetic PPAR-γ agonists were potent suppressors of epithelial proliferation and inducers of epithelial differentiation (Komuves et al., 1998; Kubota et al., 1998; Mueller et al., 1998; Rivier et al., 1998; Rivier et al., 2000; Sarraf et al., 1998; Ellis et al., 2000; Mao-Qiang et al., 2004). Our own studies confirmed the growth-suppressing effects of troglitazone, rosiglitazone, and other synthetic thiazolidinediones on human epidermal keratinocytes (Ellis et al., 2000; Bhagavathula et al., 2004; Venkatraman et al., 2004). Motility, another commonly observed feature in psoriatic keratinocytes, was also substantially down-regulated after treatment with rosiglitazone (Bhagavathula et al., 2004).

In a significant subset of patients, systemic administration of thiazolidinediones is associated with several disconcerting side effects, including fluid retention, edema, and weight gain. Although systemic delivery may be required for treatment of conditions such as type II diabetes, psoriasis is, at least in some individuals, amenable to topical therapy. If agents with PPAR-γ agonist activity could be delivered topically, many of the unwanted effects associated with systemic delivery might be averted. In the present study, we demonstrate that topical treatment of human psoriatic skin transplants on SCID mice with a novel, adamantyl-coupled...
thiazolidinedione (BP-1107) significantly reduces the hyperplasia and normalizes differentiation in the transplanted skin.

Our previous studies have demonstrated that normal human skin becomes hyperplastic as a consequence of transplantation to SCID mice (Zeigler et al., 2001). Therapeutic approaches that interfere with the immune basis of psoriasis (i.e., cyclosporine and anti-CD11a) inhibited psoriatic hyperplasia but not the hyperplasia developing in normal skin upon transplantation. In contrast, agents that interfere with the biochemical events that are directly involved in keratinocyte growth control (i.e., antibody to amphiregulin and corticosteroids) suppressed hyperplasia in both normal and psoriatic skin (Zeigler et al., 2001; Bhagavathula et al., 2005).

Not surprisingly, given what is known about PPAR-γ receptors in epidermal growth control, BP-1107 was found to suppress the reactive hyperplasia in nonpsoriatic skin transplants as well as the hyperplasia in the psoriatic skin transplants. Likewise, inhibition of human epidermal keratinocyte proliferation in monolayer was also demonstrated with BP-1107, as was down-regulation of keratinocyte motility. In these regards, the effects of BP-1107 were similar to those we have reported previously with troglitazone and rosiglitazone (Ellis et al., 2000; Bhagavathula et al., 2004), the differences being that BP-1107 functions at significantly lower concentrations than the other thiazolidinediones and works in vivo after topical application.

In addition to assessing effects on keratinocyte function, BP-1107 was also examined for effects on dermal fibroblasts. No detrimental effects on fibroblast proliferation or type I procollagen elaboration were seen at concentrations that effectively interfered with epidermal proliferation. Unexpectedly, MMP-1 (interstitial collagenase) production was significantly suppressed by BP-1107. The mechanism of MMP-1 suppression or its possible significance is not yet known. Given these actions of topical BP-1107 in the epidermis and dermis, one might expect antipsoriatic activity without the dermal atrophy associated with corticosteroid use. On the other hand, since BP-1107 seems to function at the keratinocyte level to suppress epidermal hyperplasia, there is the possibility for erosion of the reactive epidermis at the edge of the psoriatic lesion. Likewise, the possibility exists that the normal wound-healing response would be disturbed. Additional studies will be needed to determine whether these consequences materialize. Regardless, topical use of the agent is unlikely to produce a generalized effect on normal epidermal function or on wound healing.

The findings presented here may help advance understanding of how thiazolidinediones function in psoriasis. The pathophysiology of psoriasis is complex and multifaceted. A T cell-mediated immune response is involved in the initiation of psoriatic lesions, but a variety of studies suggest that intraepidermal events directly mediate hyperplastic epider-
mal growth. In particular, hyperplastic epidermal proliferation in psoriatic lesional skin is thought to reflect autocrine or paracrine stimulation through the EGF receptor. Ligands for the EGF receptor, including transforming growth factor-α, amphiregulin, and heparin-binding EGF are elevated in psoriatic lesional skin and/or in psoriatic keratinocytes relative to control skin/cells (Gottlieb et al., 1988; Elder et al., 1989; Cook et al., 1992; Piepkorn et al., 1998, 2003). Amphiregulin may be particularly important, since transgenic mice overexpressing the amphiregulin gene develop a psoriatic phenotype (Cook et al., 1997, 2004). Furthermore, our own recent studies have shown that interfering with human amphiregulin in the human skin-SCID mouse model suppresses hyperplasia in the transplanted skin (Bhagavathula et al., 2005). Although thiazolidinediones do not seem to interfere with the initial ligand-receptor-mediated events (Bhagavathula et al., 2004), by interfering with downstream signaling events (i.e., ERK1/2 activation), these agents prevent the cellular responses to EGF receptor activation that control proliferation.

Although the findings presented here strongly suggest that a direct effect of the thiazolidinediones on keratinocyte function contributes to their antipsoriatic activity, this does not rule out additional effects mediated through immune modulation. A number of PPAR-γ agonists, including members of...
the thiazolidinedione family, have been shown to be beneficial in immune/inflammatory conditions (Augstein et al., 2003; Culver et al., 2004; Hasegawa et al., 2005; Schaefer et al., 2005). Efficacy is presumed to reflect modulation of the Th1/Th2 cytokine balance. Obviously, antiproliferative activity for keratinocytes and modulation of immune function are not mutually exclusive. Additional studies will be necessary to completely delineate the relative importance of these activities to the overall antipsoriatic activity of the thiazolidinedione compounds.

In summary, the findings presented here demonstrate that a novel high-affinity PPARγ ligand, consisting of an adamantyl-coupled thiazolidinedione, reduces epidermal hyperplasia of human skin transplanted to SCID mice. Inhibition is observed after topical treatment, suggesting that effective antipsoriatic therapy may be provided without the inherent consequences observed with systemic use of this class of agents. Given these findings, it is reasonable to consider further development of BP-1107 as a topical agent for use in psoriasis and perhaps in other conditions in which epidermal hyperplasia constitutes a major part of the pathology.

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References


Fig. 8. Effect of BP-1107 on human dermal fibroblast proliferation, type I procollagen production, and elaboration of MMP-1 and -2. Top, proliferation. Primary human dermal fibroblasts were incubated in KBM with 1.4 mM Ca2+ and 1.0 μM BP-1107. Cell counts were made on days 0, 1, 2, and 3. Error bars represent means ± S.E. of three independent experiments performed in quadruplicate. No significant difference in growth was observed between control and BP-1107-treated cells. Middle, procollagen production. Condition medium from proliferation experiments was collected and assayed between control and BP-1107-treated cells. No significant difference in growth was observed. Additional studies will be necessary to completely delineate the relative importance of these activities to the overall antipsoriatic activity of the thiazolidinedione compounds.


