Core Messages

- UVB, UVA, and psoralen plus UVA (PUVA) therapy exert a variety of immunomodulatory effects on human skin.
- Induction of apoptosis in skin-infiltrating T cells is the basic mechanism in UVA phototherapy of atopic dermatitis.
- The mechanisms by which UVA-1 and UVB radiation induce T-cell apoptosis differ markedly.

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Introduction

Ultraviolet (UV) radiation has been used for decades with great success and at a constantly increasing rate in the management of skin diseases and has thereby become an essential part of modern dermatological therapy [28]. Its success as a therapeutic agent has stimulated studies about the mechanisms by which UVB and UVA phototherapy work. The knowledge obtained from this work is an indispensable prerequisite for making treatment decisions on a rational rather than empirical basis. Modern dermatological phototherapy has just begun to profit from this knowledge, and it is very likely that this development will continue and provide dermatologists with improved phototherapeutic modalities and regimens for established and new indications. This chapter aims to provide an overview about current concepts of the mode of action of dermatological phototherapy. Special emphasis will be given to studies that have identified previously unrecognized immunosuppressive/anti-inflammatory principles of phototherapy.

Historical Concepts

The prototypic skin disease showing a favorable response to UVB phototherapy is psoriasis. This inflammatory dermatosis is characterized by keratinocyte hyperproliferation. Initially, it was thought that UVB phototherapy worked through antiproliferative effects resulting from UVB-induced DNA damage [1, 2]. The number of skin diseases responding to UVB and UVA phototherapy, however, extends far beyond psoriasis. Most UV-responsive diseases are not characterized by hyperproliferative processes, but are immunologic in nature [51]. The capacity of UV radiation to affect the skin immune system was first recognized in the early 1970s in numerous studies (reviewed in [16, 23]). It is therefore now generally believed that UVB, UVA, and psoralen plus UVA (PUVA) therapy exert a variety of immunomodulatory effects on human skin, and that this is of critical importance for the therapeutic efficacy of UV phototherapy.

Therapeutic Photoimmunology

It should be noted that most of the immunomodulatory effects that have been described thus far are not specific for a single modality. At least under in vitro conditions, UVB, UVA, and PUVA radiation may have very similar or even identical immunosuppressive consequences. The actual therapeutic relevance of these effects, however, is determined by the physical properties of the type of UV radiation employed [3]. Ultraviolet B radiation mainly affects epidermal keratinocytes and Langerhans’ cells, whereas UVA radiation can penetrate more deeply into the dermis and thereby also affect dermal fibroblasts, dermal dendritic cells, endothelial cells, and skin-infiltrating inflammatory cells such as T lymphocytes, mast cells, and granulocytes (Fig. 2.1). Many of these effects have been
identified by using animal models or through in vitro studies employing cultured human skin cells. It is beyond the scope of this chapter to give a comprehensive review of photoimmunology. The reader is referred to a monograph for a more extensive discussion of immunological effects of ultraviolet radiation [23]. The emphasis will instead be on work in the field of human photoimmunology describing immunomodulatory effects of phototherapeutic relevance. In particular, recent studies employing in situ techniques in order to analyze immunomodulatory/anti-inflammatory effects that occur in the skin of patients while they undergo phototherapy will be discussed in greater detail.

In general, photoimmunological effects of therapeutic relevance fall into three major categories:
1. Effects on production of soluble mediators,
2. Modulation of the expression of cell-surface-associated molecules, and
3. The induction of apoptosis in pathogenetically relevant cells.

**Fig. 2.1a,b** Scheme of immunomodulatory effects induced by UVB (a) or UVA-1 (b) phototherapy. \textit{ICAM-1} intercellular adhesion molecule-1, \textit{IFN-\gamma} interferon-\gamma, \textit{IL-10} interleukin-10
Effects on Soluble Mediators

The beneficial effects induced by photo(chemo)therapy are thought to result from the induction of mediators with anti-inflammatory, immunosuppressive, or both properties. There is also evidence that phototherapeutic modalities suppress the production of proinflammatory cytokines. In addition, beneficial effects observed after UVA-1 phototherapy in scleroderma patients have been attributed to the production of cytokines, which upregulate matrix metalloproteinase expression in human skin. The capacity to modulate the production of soluble, immunomodulatory mediators has been demonstrated in extenso for UVB and more recently also for UVA and UVA-1 radiation [32, 36]. In contrast, little is currently known about the effects of PUVA on the release of cytokines, neuropeptides, and prostanoids.

Induction of Anti-inflammatory/Immunosuppressive Factors

Therapeutic effects induced by UVB or UVA radiation can be attributed, at least in part, to the induction of mediators with anti-inflammatory or immunosuppressive properties. In vitro studies employing cultured human keratinocytes have demonstrated that UVB, and to some extent also UVA radiation, are capable of inducing the production of cytokines, neuropeptides, and prostanoids with such properties. For example, a keratinocyte-derived cytokine of particular therapeutic relevance is interleukin (IL)-10, which is functionally defined by its capacity to suppress the production of interferon (IFN)-γ by T lymphocytes of the T helper-1-like subtype. There has been some debate about the capacity of human keratinocytes to secrete IL-10, but recent in vitro and in vivo studies have unambiguously demonstrated that UVB and, in particular, UVA-1 radiation, have the capacity to increase significantly IL-10 mRNA and protein expression in cultured normal human keratinocytes, and IL-10 protein expression is increased in epidermal keratinocytes following in vivo UV irradiation of human skin [10, 11]. Successful phototherapy (UVA-1 or UVA/UVB) of atopic dermatitis is associated with downregulation of IFN-γ expression in atopic eczema [9] and this effect may, at least in part, be explained by phototherapy-induced expression of IL-10 and subsequent paracrine suppression of IFN-γ production.

Another example of a UVB- and UVA-1-inducible soluble factor that is increasingly produced by irradiated keratinocytes and that exerts anti-inflammatory/immunosuppressive effects is the neuropeptide alpha-melanocyte-stimulating hormone (alpha-MSH). In vitro exposure of human keratinocytes to UVB or UVA-1 radiation increases the synthesis of proopiomelanocorticotropin-derived peptides including alpha-MSH [32]. Alpha-MSH has a variety of anti-inflammatory (e.g., inhibition of IL-1 or tumor necrosis factor (TNF)-α-mediated inflammation) and immunosuppressive effects (e.g., inhibition of cell-mediated immune responses). It has therefore been proposed that UV radiation-induced production of alpha-MSH constitutes a UV-inducible, anti-inflammatory agent.

A third example is UVB and UVA radiation-induced production of prostaglandins in epidermal keratinocytes [8]. Prostaglandin (PG)E₂ is a potent immunosuppressant that affects the expression of costimulatory molecules on the surface of antigen-presenting cells and thereby prevents the activation of selected T-cell subsets (especially Th1-like cells) [12].
Very recent studies indicate that in addition to keratinocytes, UV-irradiated epidermal Langerhans’ cells may constitute an important cellular source for immunosuppressive prostanoids. Ultraviolet B and, in particular, UVA-1 irradiation of human dendritic cells markedly induced cyclooxygenase activity and caused the production and release of significant amounts of PGE₂ and thromboxane (J. Krutmann et al., unpublished observation).

**Regulation of Proteolytic Enzymes by UV-Inducible Cytokines**

Ultraviolet radiation-inducible soluble factors also include cytokines such as IL-1 or IL-6, which exert proinflammatory, and thus therapeutically unfavorable, effects. It is of interest, however, that successful UVA-1 phototherapy of patients with localized scleroderma was associated with an up to 20-fold induction of matrix metalloproteinase (MMP)-1 expression in sclerotic skin lesions that had improved under phototherapy [47]. In these patients, skin sclerosis is due to increased collagen production and deposition. Phototherapy-induced softening and disappearance of sclerotic skin lesions may thus result from induction of the MMP-1 protease. Similar to UVB radiation, UVA-1 radiation might induce MMP-1 expression directly, but in vitro studies employing human dermal fibroblasts indicate that UVA-1 radiation-induced MMP-1 expression is in part caused by an autocrine mechanism involving the UVA-1-inducible cytokines IL-1 and IL-6 [52]. At least for the treatment of sclerotic skin lesions, induction of these proinflammatory cytokines by high-dose UVA-1 phototherapy may thus be beneficial rather than detrimental.

**Effects on Cell Surface Receptors**

There is increasing evidence that UVB and UVA radiation as well as PUVA treatment can directly affect the expression and function of cell surface receptors including adhesion molecules, cytokines, and growth factor receptors.

**Modulation of Adhesion Molecule Expression**

A hallmark of UV- or PUVA-responsive skin diseases such as psoriasis, atopic dermatitis, and cutaneous T-cell lymphoma is an increased expression of the adhesion molecule intercellular adhesion molecule-1 (ICAM-1) on the surface of epidermal keratinocytes [31]. The ICAM-1 molecule is functionally defined by its capacity to serve as a counter-receptor for the lymphocyte function associated antigen-1 (LFA-1), which is present on the surface of leukocytes. There is strong in vitro and in vivo evidence that ICAM-1/LFA-1 mediated cell–cell adhesion is an important prerequisite for the generation and maintenance of a variety of inflammatory and immune reactions in the skin [21, 25–28]. In healthy human skin, keratinocytes express little or no ICAM-1 on their surface. This is in sharp contrast to inflamed skin, in which keratinocyte ICAM-1 expression is markedly upregulated. Stimulation of keratinocytes by proinflammatory cytokines including IFN-γ, TNF-β, and TNF-α is responsible for this upregulation [31]. It has therefore been of particular photo-
therapeutic interest to learn that cytokine-induced ICAM-1 expression may be efficiently inhibited by irradiation of cultured keratinocytes with sublethal doses of UVB or UVA radiation [18,40].

This anti-inflammatory property of UV radiation is also observed in vivo [44,49]. Exposure of human skin to suberythemal doses of UVB radiation was sufficient to effectively suppress upregulation of keratinocyte ICAM-1 expression, which was induced through IC injection of rh-IFN-γ. In vitro and in vivo inhibition of ICAM-1 expression was observed only if UVB irradiation preceded cytokine stimulation. In additional studies, it has been demonstrated that the UVB radiation-induced suppression of ICAM-1 induction was transient in nature, because 24 h after UVB radiation exposure, significant induction of keratinocyte ICAM-1 expression was observed [20,40]. If UVB irradiation was repeated 24 h after the first exposure, reinduction of ICAM-1 suppression was achieved, indicating that a maximal anti-inflammatory effect required repetitive exposure to UVB phototherapy.

The gene regulatory mechanisms responsible for this anti-inflammatory effect are poorly understood. Inhibition of cytokine-induced ICAM-1 expression does not depend on the nature of the ICAM-1-inducing cytokine [20]. It is therefore unlikely that UVB radiation interferes with intracellular signal transduction induced by a specific cytokine, but it may very well be that UVB radiation induces a mechanism that in a more general way prevents transcription of inducible genes. The latter possibility is supported by a series of recent observations indicating that UVB radiation also suppresses the upregulation of other cytokine-inducible genes including HLA-class II molecules and IL-7 [15].

The successful treatment of psoriasis with PUVA is associated with a marked reduction in keratinocyte ICAM-1 expression in lesional skin [31]. It should be noted, however, that there is currently no convincing evidence that PUVA, similar to UVB or UVA radiation, is capable of directly modulating cytokine-induced or constitutive keratinocyte ICAM-1 expression. PUVA therapy-induced downregulation of keratinocyte ICAM-1 expression may therefore best be explained by an indirect mechanism, e.g., the reduction of cytokine-producing, skin-infiltrating inflammatory cells, which could also result in reduced ICAM-1 expression.

In addition to keratinocytes, UVB radiation has been found to significantly suppress adhesion molecule expression in antigen-presenting cells such as monocytes or epidermal Langerhans’ cells [19,45]. These downregulatory effects appear to be relatively specific, and they mainly affect the ICAM-1 molecule and members of the B7 family. UVB radiation-induced inhibition of adhesion molecule expression is of functional relevance because the resulting alteration of the costimulatory repertoire of antigen-presenting cells appears to cause anergy in effector Th1 cells and preferential activation of regulatory Th2 cells.

**Targeting of Cytokine and Growth Factor Receptors**

Keratinocyte-derived IL-1-α is one of the key cytokines in the initiation of cutaneous inflammation. The regulation of keratinocyte IL-1 receptor expression, therefore, has a major impact on the course of inflammatory reactions in the skin. Human keratinocytes express two different receptor molecules for IL-1: the IL-1 receptor type I (IL-1RI) and the IL-1 receptor type II (IL-1RII). These molecules differ markedly from a functional point
of view. IL-1RI serves as a signaling receptor, whereas IL-1RII does not mediate IL-1-induced signals. However, by virtue of its capacity to bind IL-1, IL-1RII functions as a decoy receptor limiting or suppressing IL-1-mediated tissue responses. It has, therefore, been of phototherapeutic interest to learn that UVB radiation regulates IL-1RI and IL-1RII expression differentially in human keratinocytes [13]. Expression of IL-1RII is rapidly and dramatically induced after UVB radiation, whereas IL-1RI expression decreases at the same time (though at a later point it gradually increases). It has therefore been proposed that UVB radiation may limit excessive responses to IL-1 stimulation of keratinocytes under inflammatory conditions by two complementary mechanisms:

1. Increased expression of the decoy receptor IL-1RII and
2. Decreased expression of the signaling molecule IL-1RI.

Downregulation of the signaling receptor by UVB radiation is not specific for IL-1α but may also be observed for other cytokines including TNFα. Accordingly, in vitro exposure of human keratinocytes to sublethal doses of UVB radiation initially decreased mRNA and protein expression of the 55-kDa TNF receptor, which was subsequently followed by TNF receptor re-expression, eventually exceeding baseline levels [50]. Moreover, at time points of decreased TNF receptor expression, TNF responsiveness of UVB-irradiated keratinocytes was significantly reduced. UVB radiation did not affect the release of soluble TNF receptors from human keratinocytes. In a similar manner, UVB or UVA-1 radiation also failed to modulate the production of soluble ICAM-1 molecules produced by human keratinocytes [22].

In addition to cytokines, growth factor receptors such as the epidermal growth factor (EGF) receptor appear to be important target molecules for UV radiation as well as PUVA treatment. Modulation of EGF receptor expression and function is thought to be of central importance within the signal transduction cascade relevant for UV radiation-induced gene expression. These studies were mainly directed at analyzing the so-called stress response in mammalian cells, and the UV radiation doses used were of little therapeutic relevance. This is in contrast, however, to studies assessing the effects of PUVA treatment on EGF receptor function. In murine as well as human cells, PUVA radiation inhibits binding of EGF to its receptors [30]. Since EGF is a growth factor for keratinocytes, it has been proposed that PUVA-induced inhibition of EGF binding might contribute to the beneficial effects induced by PUVA therapy in psoriasis, a skin disease characterized by keratinocyte hyperproliferation.

**Induction of Apoptosis in Skin-Infiltrating Cells**

T cells have an increased susceptibility towards UV radiation-induced apoptosis compared to other cell populations such as monocytes or keratinocytes. Morita et al. were the first to demonstrate that induction of apoptosis in skin-infiltrating T cells is the basic mechanism in UVA phototherapy of atopic dermatitis [37]. Atopic dermatitis may be viewed as a T-cell-mediated skin disease in which activation of T-helper cells by inhalant allergens (or atopens) leads to T-cell cytokine production and the subsequent development of eczema. This process involves an early initiation phase that is dominated by the expression of Th2-like cytokines, which is then switched into a second, later phase [14]. The lat-
ter is characterized by the predominance of the Th1-like cytokine IFN-γ, which is responsible for the development and maintenance of clinically apparent eczema. Successful phototherapy of atopic dermatitis with UVA-1 radiation is associated with a marked reduction in the number of skin-infiltrating T cells and subsequent downregulation of IFN-γ expression in lesional atopic skin [9]. By employing a double labeling technique to identify CD4+, apoptotic T cells, Morita et al. demonstrated that UVA-1 phototherapy induced apoptosis in T-helper cells present in the dermal compartment of atopic eczema. After only a few (1–3) exposures of patients to single doses of 130 J/cm² UVA-1, CD4+, apoptotic T cells were present in lesional atopic skin [37]. Continuation of UVA-1 phototherapy led to a gradual increase in the number of apoptotic T-helper cells, a subsequent reduction of the inflammatory infiltrate, and improvement of clinical symptoms.

Induction of T-cell apoptosis is not specific for UVA phototherapy [6, 17, 33, 55]. Successful UVB phototherapy of psoriatic patients induced a reduction in the number of skin-infiltrating T cells, which was followed by a normalization of keratinocyte morphology. In vitro UVB irradiation induced T-cell apoptosis, suggesting that the reduction of the inflammatory infiltrate resulted from UVB radiation-induced T-cell apoptosis [17]. This hypothesis has recently been proven by the demonstration of apoptotic T cells in lesional psoriatic skin of patients undergoing UVB phototherapy [41]. Induction of T-cell apoptosis was observed regardless of whether broadband UVB or 311-nm UVB phototherapy was employed. It should be noted, however, that because of its physical properties, a much greater level of 311-nm UVB radiation penetrates into human dermis, and therefore apoptosis occurs in both epidermal and dermal T cells. This difference may at least partially explain the clinical observation that 311-nm UVB phototherapy is superior to broadband UVB phototherapy for the treatment of psoriasis [42].

Induction of T-cell apoptosis is also thought to be a key mechanism for PUVA therapy. Evidence for the appearance of apoptotic T cells under PUVA therapy has thus far been provided for peripheral blood T cells in patients with Sézary syndrome undergoing extracorporeal photopheresis [55]. Interestingly, the induction of apoptotic cells is not an immunologically null event, but most likely it has immunosuppressive consequences. Phagocytosis of apoptotic cells has profound effects on mediator production by macrophages [54]. After phagocytosis of apoptotic T cells, macrophage production of the anti-inflammatory/immunosuppressive cytokine IL-10 is increased, whereas the production of proinflammatory cytokines such as TNF-α, IL-1, and IL-12 is downregulated [4, 54]. Further studies have demonstrated that inhibition of the production of proinflammatory cytokines is mediated through the autocrine production of TGF-β [34]. In addition, there is increased production of selected chemokines, in particular Mip-1-α and Mip-2. These studies provide a rationale to explain how extracorporeal photopheresis, through the induction of apoptosis in only a small percentage of circulating T cells, exerts immunosuppressive effects, as evidenced by the successful use of this modality in transplantation immunology.

The mechanisms by which UVA-1 and UVB radiation induce T-cell apoptosis differ markedly. In general, UVA-1 radiation can cause preprogrammed cell death (early apoptosis), which is protein synthesis independent, as well as programmed cell death (late apoptosis), which requires de novo protein synthesis [5]. In contrast, UVB irradiation (and also PUVA treatment) exclusively induces late apoptosis [6]. By employing atopen-specific human T-helper cells that have been cloned from lesional skin of atopic
dermatitis patients, Morita et al. have demonstrated that UVA-1 radiation is able to cause both early and late apoptosis and that UVA-1-R-induced singlet oxygen generation is the initiating event leading to T-cell apoptosis [37]. Singlet oxygen production induced the expression of Fas-ligand molecules on the surface of UVA-1-irradiated T cells. Subsequent binding of Fas ligand to Fas on the same or neighboring T cells was then shown to be responsible for T-cell apoptosis (Fig. 2.2). The key role of singlet oxygen in eliciting early apoptosis in human T cells has recently been corroborated in an independent study employing Jurkat cells. Ultraviolet A-1 radiation/singlet oxygen has been postulated to act on mitochondria and induce Jurkat-cell apoptosis by opening the megachannel and by decreasing the mitochondrial membrane potential [6]. The capacity to induce early apoptosis in mammalian cells seems to be highly specific for UVA-1 radiation and singlet oxygen, respectively.

From a phototherapeutic point of view, this qualitative difference suggests that UVA-1 phototherapy is superior to UVB or PUVA therapy for skin diseases in which induction of apoptosis in pathogenetically relevant cells is of critical importance. This assumption is supported by the observation that UVA-1 radiation, but not PUVA, is capable of inducing apoptosis in skin-infiltrating mast cells of patients with urticaria pigmentosa (Fig. 2.3). As a consequence, UVA-1 phototherapy, but not PUVA, was associated with mast cell depletion from skin and longer lasting remission periods in these patients [46, 48]. The unique properties of UVA-1 radiation have also stimulated interest in its therapeutic use for patients with cutaneous T-cell lymphoma [43]. In vitro studies indicate that malignant T cells are exquisitely sensitive to UVA-1 radiation-induced apoptosis, and UVA-1 phototherapy might thus prove to be at least equivalent, if not superior, to PUVA for this indication [38].

![Fig. 2.2 Scheme of potential mechanisms by which T-cell apoptosis may be induced. sFASL soluble Fas ligand](image)
Fig. 2.3a,b Apoptotic mast cells in lesional skin of a patient with urticaria pigmentosa before (a) and after (b) UVA-1 phototherapy (3 × 130 J/cm²). Mast cells were stained with an anti-mast-cell tryptase antibody in red, and apoptotic cells were detected by the transferase mediated d-UTP nick end-labeling (TUNEL) method in green. Apoptotic mast cells thus stain orange.
Photobiological Aspects of Photo(chemo)therapy

Several immunomodulatory effects of phototherapeutic relevance, e.g., the induction of IL-10 or the suppression of ICAM-1 induction, may be achieved by both UVB and UVA-1 irradiation. The photobiological mechanisms responsible for these immunomodulatory effects, however, have been found to greatly differ depending on the type of UV radiation used [24].

Similar to antiproliferative effects, immunomodulation induced by UVB radiation appears to result from UVB radiation-induced generation of DNA photoproducts, in particular thymine dimers. UVB radiation-induced suppression of IFN-γ-stimulated keratinocyte ICAM-1 expression was associated with the formation of significant numbers of thymine dimers in UVB-irradiated human skin [49]. Topical application of a DNA repair enzyme encapsulated into liposomes not only decreased the number of thymine dimer positive keratinocytes in irradiated skin by about 40–50%, but it completely prevented UVB radiation-induced inhibition of ICAM-1. Essentially identical results were obtained from in vitro studies, in which the role of thymine dimer formation for UVB radiation-induced IL-10 expression in cultured murine keratinocytes was assessed [39]. Exposure of murine keratinocytes (PAM212 cells) to increasing doses of UVB radiation dose-dependently increased both thymine dimer formation and IL-10 protein expression, and treatment of irradiated cells with exogenously supplied DNA repair enzymes was sufficient to partially reduce the number of thymine dimers and at the same time to completely suppress UVB radiation-induced IL-10 protein synthesis. The precise reason for the discrepancy between the partial reversal in thymine dimers and the total prevention of immunomodulatory effects such as IL-10 synthesis or inhibition of ICAM-1 induction is currently unknown. It has been postulated that gene-specific repair mechanisms may explain this phenomenon. Thus, formation of thymine dimers appears to be of central importance for UVB radiation-induced therapeutic effects. It should be noted, however, that UVB radiation might also have cell membrane effects independent of DNA damage [29].

In contrast to UVB radiation, UV A-1 radiation-induced immunomodulatory effects are thought to be based on oxidative mechanisms [22]. The generation of singlet oxygen plays a prominent role. This conclusion is based on the following three observations: UVA radiation-induced gene-regulatory events such as the regulation of ICAM-1 or collagenase I expression can be
1. Inhibited by singlet oxygen quenchers,
2. Enhanced through strategies that result in an increase in the half life of singlet oxygen, and
3. Mimicked by stimulation of unirradiated cells with singlet oxygen-generating systems [7, 53].

Of central importance to the understanding of these mechanisms is the recent finding that both UVA radiation- and singlet oxygen-induced gene expression are mediated through activation of transcription factor AP2, and that UVA radiation-induced gene expression is controlled through the balance between AP2 and its alternative splice product AP2B [7]. Singlet oxygen, however, is not only an important mediator for UVA radiation-induced
gene regulatory events, but also plays a key role in UVA radiation-induced apoptosis in human T-helper cells [37].

In contrast to UVB or UVA radiation-induced immunomodulation, the photobiological base for PUVA-induced immunosuppressive effects has not yet been characterized.

**Perspectives**

There is compelling evidence that the efficacy of photo(chemo)therapy may not simply be attributed to antiproliferative effects, but most likely involves immunomodulatory consequences, some of which have been outlined above. It should be noted, however, that the majority of photoimmunological studies have been conducted either in vitro or in animal models, whereas only recently have in situ techniques been employed in order to monitor immunological changes induced in the skin of patients undergoing UV phototherapy. These studies have already contributed to our knowledge about the mode of action of UVA and UVB phototherapy, e.g., by identifying apoptosis as a key mechanism in phototherapy of T-cell-mediated skin diseases. This progress should prompt further interest in studies in this area of clinical research, which might best be described as “therapeutic phot-immunology”.

**References**


