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REVIEW ARTICLE

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Treatment of pemphigus and other neglected skin conditions with PC111, a human anti-Fas Ligand monoclonal antibody: a potential disease modifier

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ABSTRACT

Background: Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease with high morbidity and mortality, treated mainly with long-term immunosuppressants. Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is an acute, life-threatening drug reaction with severe skin and mucosal involvement. No approved therapies currently exist for SJS/TEN.

Aim: To demonstrate that the soluble form of Fas ligand (sFasL) is a relevant therapeutic target in both PV and SJS/TEN, and to provide evidence that PC111, a fully human monoclonal antibody against sFasL, is effective in both conditions.

Evidence review: In PV, autoantibodies (PVIgG) target desmogleins, leading to blistering via signaling cascades. sFasL, released upon PVIgG binding, contributes to this process by promoting desmoglein degradation and acantholysis. In SJS/TEN, elevated sFasL induces keratinocyte apoptosis, contributing to epidermal detachment.

Findings: PC111 blocks acantholysis and blister formation in PV through a local, rapid mechanism, downstream of the immune system, thus differentiating from the currently used immunosuppressive treatments. In SJS/TEN, PC111 prevents keratinocyte apoptosis induced by patient serum and improves ocular symptoms in a mouse model. Its fast action suggests potential for early intervention to halt disease progression.

Conclusions: PC111 may act as a disease-modifying agent, promoting long-term remission in PV and preventing progression in early-stage SJS/TEN.

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Dermatology; drug response; anti-Fas Ligand; pemphigus; SJS/TEN

Introduction

Over the past 20 years there has been a revolution in dermatology thanks to the unveiling of disease pathomechanisms, which have allowed the design and testing of several new targeted therapies that have completely changed the perspectives and quality of life of patients. This is particularly the case for the two most common inflammatory skin disorders, atopic dermatitis (AD) and psoriasis (Pso), which are affecting millions of people around the globe (1, 2) The new drugs are safe and effective, at least for specific groups of patients, and lead to complete remission either on therapy or after its cessation, thus partially fulfilling the concept of 'disease modification' (3).

AD and Pso are characterized by a complex pathophysiology, including genetic background, innate as well as adaptive immunity, with the involvement of different lymphocyte subpopulations and cytokines (4, 5). The pathomechanisms underlying Pso are more uniform and have been better analyzed, as compared to AD; hence, therapy-free remission has been achieved, at least in part, only in psoriasis. This implies that the more complex the pathophysiology, the more difficult it is to discover and develop disease modifying drugs. In any case, it is obvious that disease modification could not be achieved with the broad immunosuppressive therapies that have been used so far, such as cyclosporine and methotrexate, but only with new available, safe, and effective targeted therapies (6, 7).

In addition to AD and Pso, there is a spectrum of less common, immune-inflammatory skin conditions where the pathophysiology is only partially understood, and the discovery and development of new drugs is still difficult. However, the triggering pathomechanisms underlying autoimmune bullous disorders have indeed been largely explored and defined, being less complex than those in AD and Pso. In particular, the target antigens of the autoantibodies in pemphigoid and pemphigus are well characterized (8). In pemphigus, the most severe autoimmune bullous disease, binding of autoantibodies to the target antigens on keratinocytes triggers several signaling pathways, leading to the formation of the characteristic blisters. Despite these discoveries, pemphigus treatment still relies on the use of potent and broad immunosuppressors (such as Rituximab and steroids) (9), often associated with severe or lethal side effects, similarly to the pre-biologics era in AD and Pso with cyclosporine and methotrexate. Thus, pemphigus treatment has still a high unmet medical need, since only the

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availability of targeted therapy would allow a long-term control of the disease and, potentially, a disease modification.

PC111 is a fully human IgG4, kappa, monospecific, bivalent antibody that specifically recognizes soluble Fas ligand (sFasL) (manuscript in preparation), which has been identified as a critical factor in the pathogenesis of pemphigus (10). The Fas/FasL system belongs to the tumor necrosis factor superfamily and, by inducing apoptosis, is involved in autoimmunity and cancer (11). This review will discuss the reasons why PC111, by blocking sFasL, will be the first targeted therapy for pemphigus, acting at the local level downstream of the immune system, thus differentiating itself from the current available treatments based on broad immunosuppression. The potential efficacy of PC111 in the treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis will also be presented, due to its sFasL-based pathogenetic mechanism.

Pemphigus

Pemphigus is a chronic autoimmune blistering disease affecting both the skin and the mucous membranes. Pemphigus is characterized by the presence in patients' sera of IgG autoantibodies (PVIgG) directed against the adhesion molecules (desmogleins, Dsgs) contained in the intercellular junctions of keratinocytes (desmosomes), leading to cell-to-cell detachment (acantholysis) and the consequent formation of the blister (12).

Pemphigus can be divided into three major variants: pemphigus vulgaris (PV), pemphigus foliaceous (PF), and paraneoplastic pemphigus (PNP).

PV is characterized by the presence of autoantibodies directed against Dsg3 and Dsg1. In most cases, PV initiates with painful erosions in the buccal mucosa, resulting in difficult feeding and weight loss. Erosions may also involve the larynx with hoarseness and, less frequently, the esophageal, conjunctival, and genital mucosae. PV patients often present intact flaccid cutaneous blisters that frequently expand into large erosions affecting considerable areas of the skin, with consequent risk of infections.

PF patients' sera contain autoantibodies against Dsg1 and affect only the skin, without mucosal involvement. Lesions consist of crusted and scaly erosions on erythematous skin mainly affecting the seborrheic areas, but potentially expanding to become an exfoliative erythroderma. Flaccid blisters are rarely observed. PF can be initially misdiagnosed with seborrheic dermatitis (13). An endemic variant of PF (*fogo salvagem*) has been reported in rural areas of Brazil, Colombia, Morocco, and Tunisia, possibly caused by various insects (14).

PNP is a rare form of pemphigus always associated with underlying neoplasms, most frequently, hematologic malignancies. Autoantibodies are directed against various antigens, including not only Dsgs, but also plakins that link the cytoskeletal network to desmosomes. PNP is typically characterized by painful stomatitis and erosions of the buccal mucosa and oropharynx. Ocular and genital mucosa can also be affected. The skin displays vesicles and blisters, papules and erythema, always appearing after mucosal involvement (15).

It is estimated that 60–90% of pemphigus cases are PV, while 10%–20% of patients are PF, depending on the geographic area. PNP accounts for about 5% of pemphigus cases (16,17).

The incidence rate of PV ranges annually between 0.76 cases per million in Northern Europe and 36 cases per million in Jewish individuals in the United States. PV is predominantly present in the Middle East, with the highest incidence in Israel and Iran. Pemphigus is associated with a high mortality rate ranging between 5% and 30%, mostly because of infections and treatment side effects. In general, mortality among patients with pemphigus is 2.4-times greater than for the general population (18).

Pemphigus patients' sera contain Ig autoantibodies that bind to Dsgs and play a pivotal role in the pathomechanisms of the disease. Numerous studies have demonstrated that antigen-autoantibody binding directly causes epidermal acantholysis through several mechanisms, leading directly to Dsg dysfunction and depletion, loss of desmosomal integrity and adhesion (19). This model of steric hindrance has been questioned by the discovery of autoantibody-triggered signaling pathways (20), including p38 mitogen-activated protein kinase (MAPK) that modulates intermediate filaments and interferes with the maintenance of the desmosomal structure (21). However, inhibiting p38 does not prevent blister formation (22), while a clinical trial of a p38 inhibitor in pemphigus (NCT00606749) was terminated owing to toxicity and limited efficacy (8). Autoantibodies can also trigger other molecules, such as EGFR (23) and MYC (24), but none of these factors can induce acantholysis (25).

The role of cell apoptosis in pemphigus has been a matter of debate, as to whether this event precedes the formation of the blister or is just a secondary event (26,27). Yet, a relevant body of evidence supports the concept that keratinocyte cell death is a critical event during acantholysis (20). First, a genome-wide association study mapping PV patients demonstrated that a single nucleotide polymorphism (SNP) of the ST18 gene is significantly associated with PV and regulates apoptosis (28). ST18 enhances PVIgG-induced loss of keratinocyte adhesion (29) and decreases Dsg expression (30). Puviani and colleagues first identified the presence of TUNEL positive cells in pemphigus patients' skin before keratinocyte detachment (31).

The finding of keratinocyte death being expressed in perilesional and prelesional pemphigus skin was confirmed in several studies (32,33). In addition, Pelacho and coworkers showed that PVIgG activate caspases and induce apoptosis in human keratinocytes (34). The injection of PVIgG in the passive neonatal mouse model of pemphigus induces the expression of caspases and apoptotic cells before the appearance of the blisters (35). Finally, anti-mitochondrial antibodies act synergistically with PVIgG to elicit the process of programmed cell death and detachment of epidermal keratinocytes, termed apoptolysis (36).

There are several distinct subtypes of apoptosis that, although morphologically similar, can be triggered through different biochemical routes, for example the intrinsic and extrinsic pathways (37). The extrinsic apoptotic pathway is classically mediated by death receptors, including Fas and its ligand. Fas Ligand is a transmembrane protein (mFasL) that can be proteolytically cleaved to generate its soluble form of 26 kDa (sFasL) (38). Both forms of FasL can bind to the receptor, Fas, exerting different activities, both apoptotic and pro-inflammatory ones. While mFasL is essentially associated with T lymphocyte apoptosis and constitutes the guardian against autoimmunity and cancer, sFasL promotes autoimmunity and pro-inflammatory activities (39). In tissues different from the immune system, sFasL is able to induce cell death in a sort of tissue-specific, autocrine/paracrine loop, and thus able to affect functions that are peculiar for that tissue (40). In healthy skin, FasL is localized in the basal layer and in the first supra-basal layers of the epidermis, and homogeneously distributed within the cytoplasm in association with intermediate filaments (41), while Fas is expressed at the membrane level in basal and immediately supra-basal keratinocytes (42).

FasL and pemphigus: target validation

There is an expanding body of evidence on the role of the Fas/FasL system in pemphigus. Both Fas and FasL have been detected in lesional skin (43,44). While, in normal epidermis, Fas expression is limited to the surface of basal cells, in pemphigus lesions it is also detected in supra-basal layers, even before cell detachment (10). In a recent microarray analysis, Starr and coworkers found an up-regulation of the genes associated with the Fas/FasL pathway in canine lesional pemphigus skin (45).

Our group first demonstrated that FasL levels are upregulated in untreated pemphigus patients' sera, as compared to sera from healthy subjects, while corticosteroids revert FasL to normal levels after two-week therapy. In the same experiment, we showed that patients' sera-induced keratinocyte apoptosis was inhibited by anti-FasL neutralizing antibodies, indicating that FasL contained in pemphigus sera is responsible for keratinocyte death, *via* caspase-8 activation (31). The crucial role of FasL in pemphigus was confirmed by the observation that PVIgG up-regulated FasL mRNA in keratinocytes and induced its release from the same cells (46). In addition, PVIgG treatment was shown to induce a co-aggregation of FasL and Fas receptor with caspase-8 in the formation of the Death-Inducing Signaling Complex (DISC), which in turn leads to the activation of the effector caspase-3 and -7 (47), thus strongly suggesting that PVIgG trigger the Fas-FasL system followed by apoptosis in human keratinocytes. Not only FasL causes apoptosis, but it is also a critical step in mediating PVIgG-induced acantholysis. In fact, FasL synergizes with PVIgG in the induction of acantholysis in an organ culture model of pemphigus (48). Moreover, recombinant FasL provokes the activation of caspase-8 followed by the activation of caspase-3, when Dsg3 is still intact. Dsg3 cleavage and degradation with progressive cell-to-cell detachment occurs immediately after keratinocyte apoptosis. Keratinocyte acantholysis induced by PVIgG in the dissociation assay was prevented by the addition of an anti-FasL neutralizing antibody, while blocking FasL by siRNA inhibited Dsg degradation and caspase-3 activation, indicating that FasL plays a critical role in acantholysis *in vitro* (10).

Lotti and coworkers showed that only sFasL is responsible for blister formation in pemphigus. Indeed, in neonatal mice lacking the sFasL gene, no acantholysis and blister formation was detected upon injection of PVIgG, as determined by histology and the measurement of the relative acantholytic area. On the contrary, acantholysis was clearly observed in mice lacking mFasL and in wild-type animals, indicating that only sFasL is indispensable for blister formation in a validated pemphigus mouse model (10).

Blocking FasL inhibits blister formation *in vivo*

The critical role of FasL in pemphigus was confirmed by the injection of PVIgG in neonatal wild-type mice followed by the administration of an anti-FasL blocking antibody. PVIgG provokes the formation of intraepidermal blister and the deposition of autoantibodies, recapitulating the immune-histologic alterations of pemphigus in humans (49). PVIgG also induced the rapid up-regulation of FasL in mouse epidermis, before the formation of the blisters. When anti-FasL was administered 1 or 2 h (h) after PVIgG, blisters started to decrease to eventually disappear at 3 h after induction, as shown by hematoxylin and eosin staining and by the measurement of the relative acantholytic area. Mice were also treated at 3 h, with different doses of anti-FasL Ab, which inhibited blister formation in a dose-dependent manner (10). This indicates that blocking FasL prevents blister formation *in vivo*.

Lotti and coworkers were also able to generate an active pemphigus mouse model recapitulating different forms of the disease based on the production of autoantibodies against the various target antigens (50). For instance, Dsg3$^{-/-}$ mice were inoculated with recombinant Dsg3 to induce the production of autoantibodies. Splenocytes were then transferred into immunodeficient Rag2$^{-/-}$ mice that produce antibodies against endogenous Dsg3, thus displaying the appropriate phenotype. The combined Dsg1/Dsg3 model exhibited the most severe disease. The *in vivo* active model not only recapitulates the complexity of pemphigus, but also allows evaluation of the long-term benefits and the potential side effects of experimental drugs. It was recently shown that the administration of methyl-prednisolone every day for 4 weeks at a very high dose significantly reduced the PV score, counteracted the mouse weight loss, and allowed a prolonged survival rate in treated mice (50). Using the same model, our group demonstrated that an anti-murine FasL antibody was capable of reducing the PV score, counteracted weight loss, and prolonged the survival rate (Figure 1).

This compelling evidence supporting the proof of concept that FasL is a critical factor in the pathogenesis of pemphigus and that its blockade inhibits blister formation *in vitro* and in the two above pemphigus mouse models was obtained using an uncharacterized FasL antibody specific for murine FasL.

PC111 efficacy in human models of pemphigus

PC111 is a fully human anti-FasL antibody that does not recognize the murine FasL. Several in-vitro, ex-vivo, and in-vivo experiments were carried out to confirm that the anti-human FasL antibody

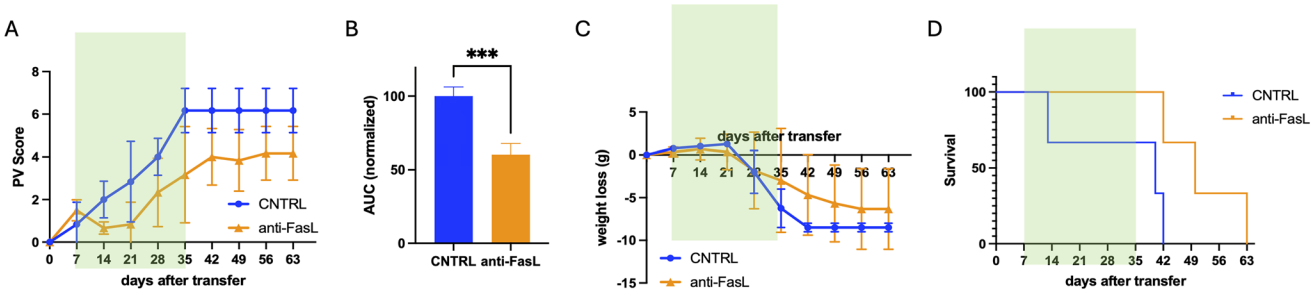

Figure 1. Effects of anti-FasL antibody administration in the active pemphigus mouse model (DSG1/DSG3 autoreactive model). Anti-FasL antibody directed against murine FasL was administered intra-peritoneally twice weekly from day 7 after the adoptive transfer to day 35 (green shaded area). Animals were randomly assigned to the anti-FasL or control (CNTRL/PBS) treatment group ($n=3$ animals per group). PV score (A) and body weight variations (C) were reported weekly, till day 63. (B) PV score overtime was translated in area under the curve (AUC), normalized to CNTRL. By unpaired *t*-test analysis, anti-FasL group is statistically different from CNTRL group ($p=0.0007$). (D) Survival curve overtime. With log-rank (Mantel-Cox) test analysis, $p=0.06$, with a median survival of 40 days for CNTRL group and 50 days for anti-FasL group.

PC111 can block blister formation in a human setting. To this extent, monolayers of keratinocyte cultures were fragmented by the addition of PVIgG, resulting in acantholysis. PC111 dose-dependently reduced fragmentation, as shown by the measurement of the keratinocyte dissociation score (51). This was the first demonstration that PC111 inhibits acantholysis in a human model of pemphigus *in vitro*, in agreement with previous observations showing that FasL cooperates with PVIgG to cause acantholysis in a human setting (48).

PC111 efficacy in blocking blister formation was also confirmed in an ex-vivo model of pemphigus that allows to preserve human skin architecture. Human skin organ cultures (HSOC) from skin biopsies were injected with either scFv antibody fragment against Dsg1 and Dsg3 (52), resulting in an extremely severe form of acantholysis, or with a pool of autoantibodies from pemphigus sera, resulting in a milder acantholysis, likely more similar to the presentation of pemphigus in patients. In both experiments, PC111, injected after the induction of the blisters in a curative rather than in a preventive manner (53), inhibited acantholysis, further indicating that blocking FasL prevents blister formation also in a human pemphigus model (54).

On the basis of this evidence, our group sought to demonstrate the efficacy of PC111 *in vivo*. However, on one hand mice with defective Fas or FasL signaling exhibit target-related pathology (55), confirming the relevance of mouse as a species to study the pharmacology of FasL blockade; on the other, PC111 is a human antibody that does not bind murine FasL. To overcome this obstacle, we generated a transgenic humanized FasL mouse model (manuscript in preparation); in this proprietary model, PC111 significantly reduced acantholysis induced by the injection of PVIgG in neonatal mice, the validated, gold standard model for drugs aiming at pemphigus treatment.

Together, the *in vitro*, ex-vivo, and *in vivo* data clearly demonstrate the efficacy of PC111 in humanized models of pemphigus (Figure 2).

PC111 differentiates itself from current pemphigus therapies

For many years systemic corticosteroids and immunosuppressants have been the basis of pemphigus therapy. Although these drugs have limited the severity of the disease and saved patients' lives, as compared to the pre-steroid era, patients need to be treated for life leading to chronic immunosuppression associated with severe adverse events and, in a sizeable 5-15% of cases, to death. Since 2020, Rituximab (RTX), an anti-CD20 monoclonal antibody that depletes B-cells and lymphoid resident memory B-cells, has been approved as first-line treatment for PV, in combination with systemic corticosteroids (56).

RTX is a highly effective therapy in pemphigus, as shown by clinical trials and by real-world data (57). Yet, it presents several limitations, including a median time to achieve remission of 3–6 months on average and a temporary therapeutic effect (58). Moreover, 40%–80% of the patients relapse following RTX (59), after a remission ranging from 6 to 24 months (60), and only a small percentage of cases maintains remission off therapy (58, 59).

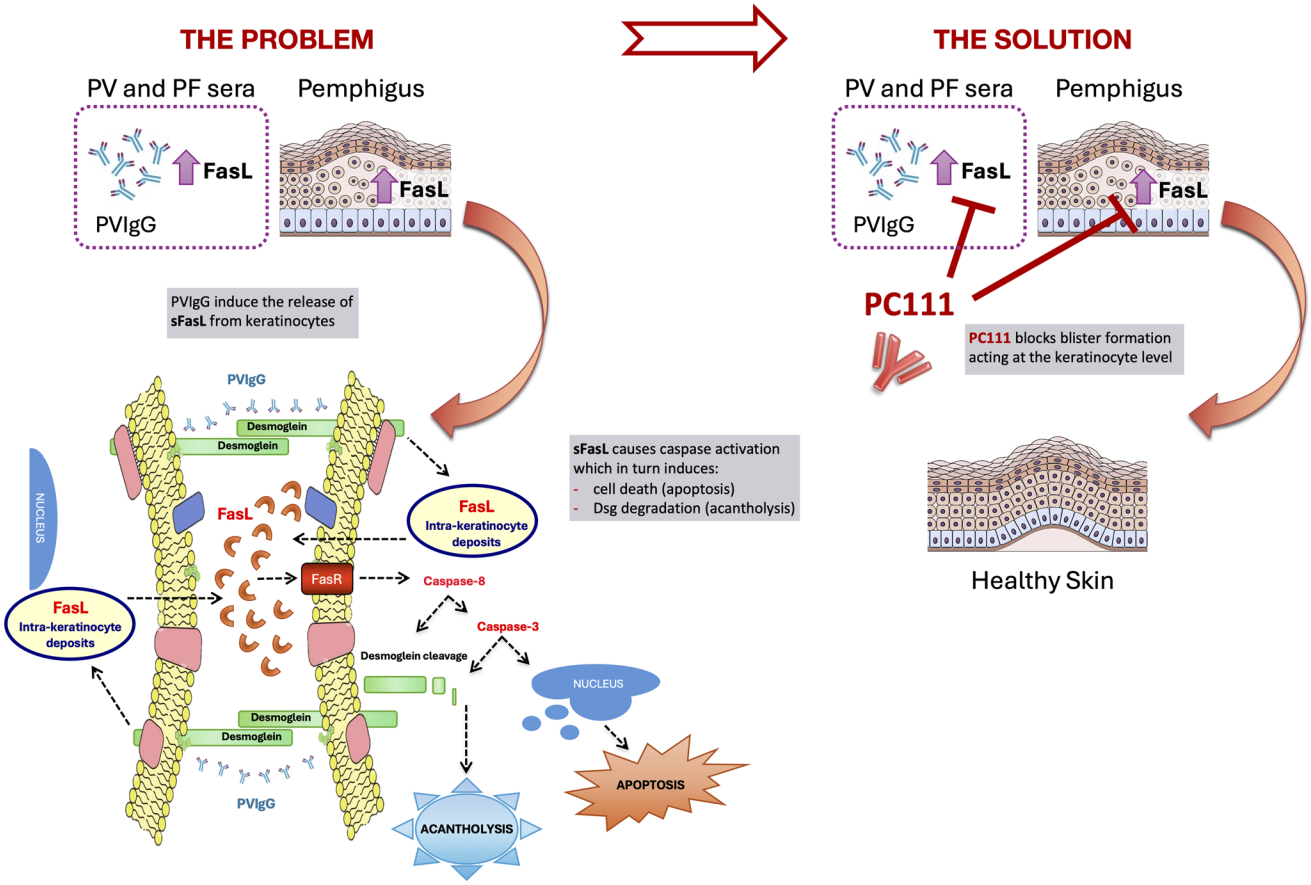

Figure 2. Schematic representation of the mechanism of action of PC111 in pemphigus. Soluble FasL induces blister formation through activation of apoptosis and desmoglein (DSG) degradation (the Problem). PC111 blocks the blister formation and restores skin integrity (the Solution).

These findings are associated with the need of repeated infusions for disease control, leading to chronic immunosuppression and serious adverse events (61). Finally, according to a recent study, mucosal involvement, a key feature of patients with PV, is a high-risk factor for poor outcome and relapses of PV patients treated with RTX (62).

Conversely, PC111 is the first targeted, non-immunosuppressive therapy for PV, acting at the epidermal level by blocking the function of FasL released from keratinocytes, and is expected to provide a rapid clinical response through a quick onset of action (10). PC111 can potentially achieve clinical remission more rapidly than RTX, without any use of steroids or allowing an earlier and substantial lowering of their dose; such an non-immunosuppressive mode of action will avoid the serious adverse effects associated with either RTX or corticosteroids. Because of its unique mechanism of action, PC111 will also differentiate itself from the other immunosuppressive drugs normally used as adjuvants in the treatment of pemphigus, including Azathioprine, Cyclophosphamide and Mycophenolate mofetil (reviewed in Ref. (25)). High-dose intravenous immunoglobulins (IVIg) have been used successfully as an adjuvant therapy to corticosteroids, RTX and other immunosuppressive drugs in resistant forms of pemphigus (63,64). Although the mechanism of action is not fully understood, IVIg are known to block Fc receptor, different T-cell functions, and induce B-lymphocyte apoptosis (65). IVIg-related adverse events have been described, including infections, acute renal failure, and thrombosis (66–68) (Table 1).

Furthermore, all the emerging therapies in development for Pemphigus are designed to interfere with the immune system (reviewed in Ref. (9,25)). Bruton-kinase (BTK) inhibitors, a promising anti-B-cell therapy, and efgartigimod, that targets neonatal Fc receptor thus blocking IgG recycle by inducing autoantibody catabolism, failed to meet their primary efficacy endpoints in phase 3 trials (NCT03762265, NCT03334058). These results have led to the discontinued development of these molecules. Chimeric autoantibody receptor (CAAR)-T cells therapy, that targets anti Dsg3 B-cells, is a promising and novel approach for the treatment of Pemphigus; yet, it fails to target anti-Dsg1 autoantibodies that play a critical role in the disease. In addition, the cost of this therapy is exorbitant, while a complex intravenous administration protocol including other immunosuppressors will make it very difficult to achieve adequate patients' compliance. In 2020, a phase I trial was started (NCT04422912), but no results have been released so far. Finally, it is worth mentioning that in early 2024, the FDA mandated a black-box warning for any CAAR-T cell therapy, because of their risk of secondary T-cell malignancies. TPM203, anti-autoreactive T-cells conjugated to nanoparticles was generated to block pathogenic anti-Dsg3 IgG. A phase I trial was recently completed (TPV11), while it is not known whether the development of the technology will be continued. (Figure 3).

As recently reported by the International Pemphigus and Pemphigoid Foundation, together with a group of key opinion leaders, Pemphigus treatment is still a high unmet need (69). In this paper, it is clearly stated that '*The ideal goals of treatment are to have complete healing of blisters and resolution of the functional impairment associated with the disease, improve QOL, prevent disease recurrence, and limit treatment side effects related to corticosteroids and immunosuppressants*'. That is why patients strongly need a novel drug that meets these criteria: PC111, by acting rapidly and effectively downstream of the immune system, achieves adequate disease control, avoids adverse events related to chronic immunosuppression and allows for a prolonged administration, similarly to currently used targeted therapies for other inflammatory skin diseases.

Stevens-Johnson syndrome/toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) encompass a spectrum of cutaneous adverse drug reactions of different severity, with life-threatening effects and long-standing sequelae (70). Mortality rate ranges between 1 and 5% in SJS and 25–35% in TEN (71). Cutaneous involvement consists of erythematous macules and target lesions that become confluent to progress to flaccid blisters and large areas of denuded epidermis (72). Most patients have mucosal involvement that is particularly harmful at the ocular level, eventually leading to blindness (73).

There is no approved drug, nor standardized guidelines for the treatment of SJS/TEN. In addition to withdrawal of the causative drug and hospitalization for supportive care, many medications have been used with controversial results, including corticosteroids, cyclosporine, anti-TNFa antibodies, and IVIg (74). Recently, seven patients with SJS/TEN were successfully treated with JAK inhibitors (75). (Figure 4).

SJS/TEN is a severe T-cell mediated type IV hypersensitivity reaction triggered by medication exposure in the vast majority of cases (76). The key event in the pathogenesis of SJS/TEN is the activation of T cells, followed by the production of cytokines/chemokines, resulting in keratinocyte apoptosis (reviewed in Ref.

Table 1. PC111 differentiates itself from current pemphigus therapies.

Therapy	Origin of the mAb	Mode of action	Site of action	Onset of action	Complete remission	Duration of response	Side effects
Systemic steroids	N/A	Immunosuppressive	Systemic	Rapid	Rapid	N/A[b]	Severe
Rituximab + steroids	Chimeric (murine/human)	On-target, Immunosuppressive and steroid-sparing	Systemic	Slow	3–6 months	40–80+% relapses after 14–16 months	Severe
Immunosuppressive adjuvants	N/A	Immunosuppressive and steroid sparing	Systemic	N/A[a]	N/A[a]	N/A[a]	Severe
Adjuvant IVIg	Fully human	Immunomodulating	Systemic	N/A[a]	N/A[a]	N/A[a]	Severe
PC111	Fully human	On-target, NON-immunosuppressive and steroid-sparing/eliminating	Local	Rapid^	TBD (expected rapid)[c]	TBD (based on neutralized sFasL levels)	TBD (not related to immune suppression)

N/A: not applicable.
TBD to be determined.
[a]administered with other therapies.
[b]steroids are administered chronically, at various doses.
[c]based on in-vivo data (see reference no. 10).

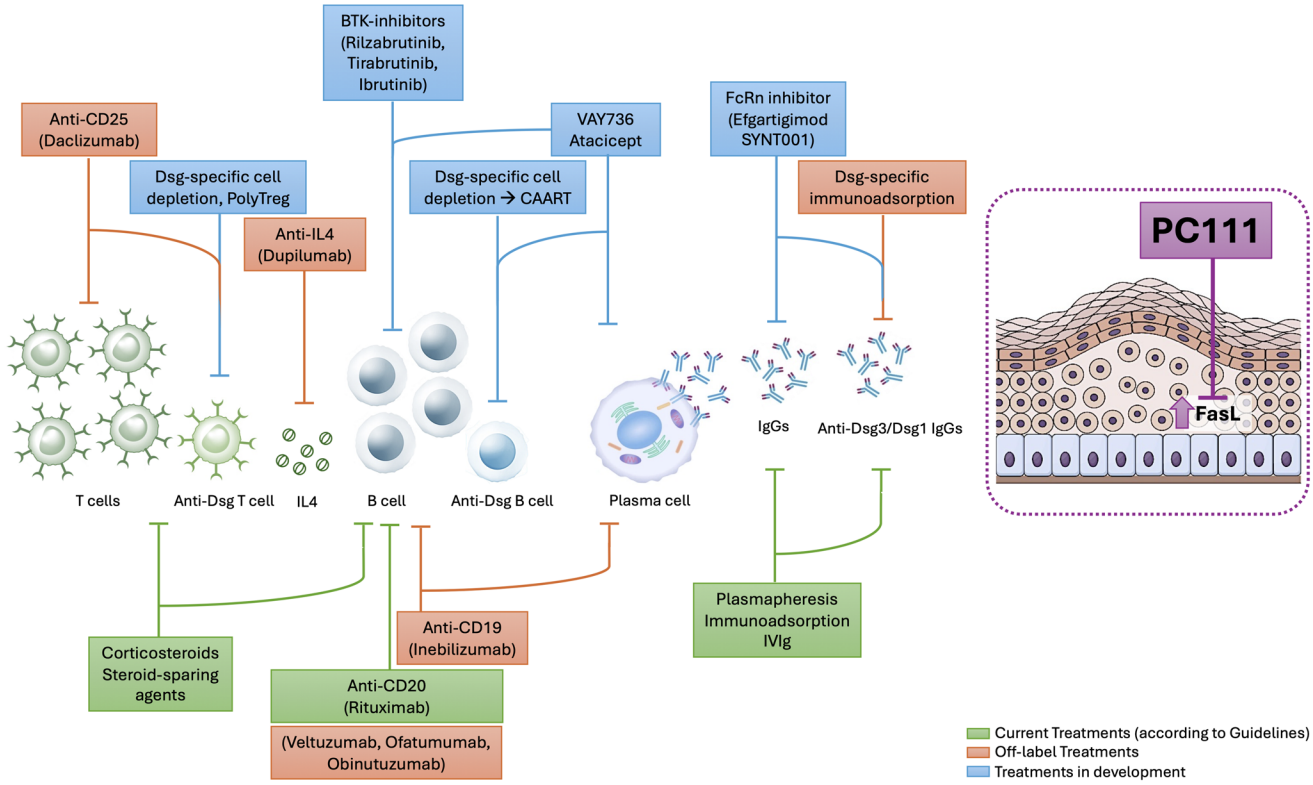

Figure 3. Overview of current (approved or off-label) therapies and new therapeutic approaches for pemphigus treatment. Therapeutic strategies are outlined based on their mechanisms of action. Whereas conventional and under development treatments affect the immune system, PC111 is the only agent working downstream of the immune system, acting at the keratinocyte level, where blisters are formed.

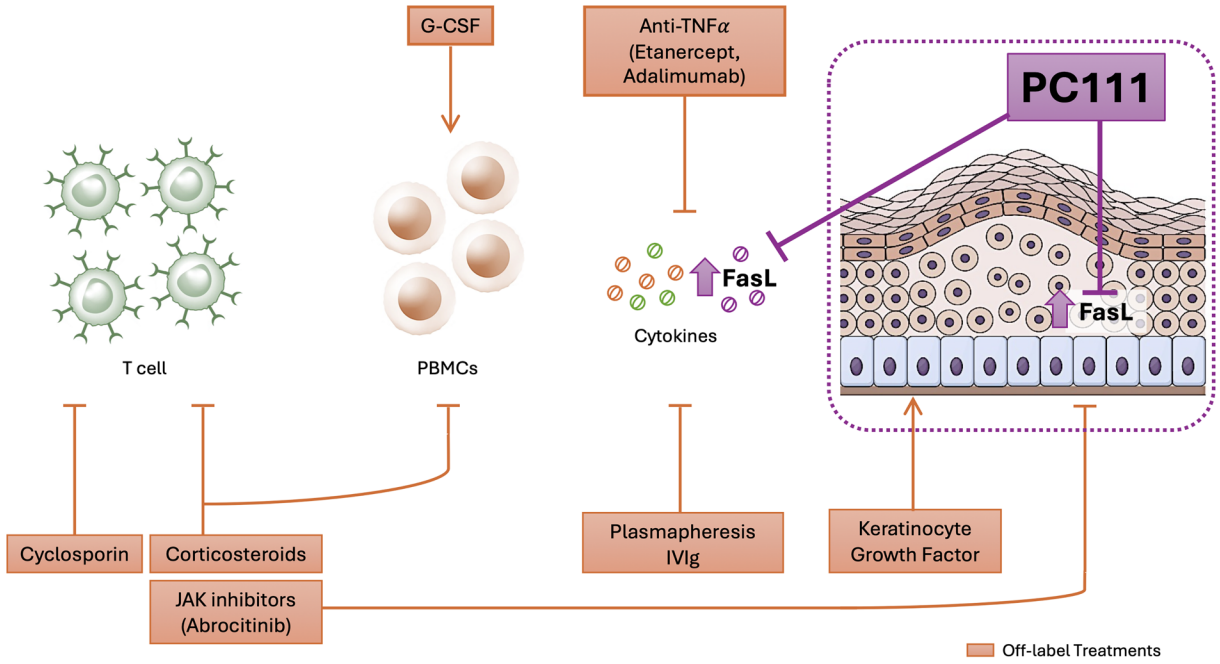

Figure 4. Overview of current (all off-label) treatments for SJS/TEN treatment. Therapeutic strategies are outlined based on their mechanism of action. Unique positioning of PC111, which is acting at the keratinocyte as well as at the serum level in SJS/TEN.

(77,78)) Among various factors, the Fas/FasL system has been shown to play a major role in the pathomechanisms underlying SJS/TEN. Indeed, sFasL levels are elevated in SJS/TEN patients, as compared to either healthy controls or patients with erythema multiforme (79–81). Moreover, peripheral blood mononuclear cells obtained from patients with SJS/TEN, upon stimulation with the causal drug, secrete high levels of sFasL (82), while sera from patients induces apoptosis in cultured keratinocytes (83). Finally, FasL expressed by SJS/TEN keratinocytes causes keratinocyte apoptosis in either an autocrine or a paracrine fashion (79,84).

PC111 efficacy in models of SJS/TEN

Against this background, blocking sFasL could be a successful treatment strategy in SJS/TEN. In fact, it was previously shown that sFasL levels are markedly elevated in the very first days of the disease, to then decline after 5–6 days (85). Given the rapid onset of action of PC111, the drug could be administered intravenously immediately after the diagnosis of SJS/TEN to block the progression of the disease. This therapeutic hypothesis was tested and, indeed, PC111 dose-dependently abrogated SJS/TEN serum-induced cell death in human keratinocytes; furthermore, PC111 prevented conjunctivitis in a mouse model induced by injecting SJS/TEN PBMC's + causative drug and inhibited apoptosis of the conjunctival epithelium in the same animals (86).

Blocking sFasL in the very first days would modify the natural course of the disease, by impeding the spread of skin lesions, thus preventing skin sloughing and denudation that lead to infections and systemic organ involvement, ultimately reducing the risk of death. Finally, a rapid intervention would lead to a quicker recovery, thus reducing the costs experienced by patients and the healthcare expenditures.

Conclusions and perspectives

In the last twenty years targeted therapy has revolutionized the treatment of several diseases in all fields of medicine. In dermatology, targeted therapy has completely changed the quality of life of a huge number of patients suffering from Pso, AD, as well as other less frequent skin conditions (87–89). Drugs designed to block different components of the pathomechanisms underlying those diseases have allowed a protracted treatment, leading to partial or complete remission, without the side effects normally associated with the use of broad immunosuppressors. Likewise, given its rapid and non-immunosuppressive mode of action, PC111 could be administered for a long time to achieve and maintain remission in pemphigus, with great satisfaction of the patients. In addition, PC111 may be given as a bridge therapy, before RTX achieves clinical remission or even in combination with it, given their independent and synergistic mechanisms of action. Nonetheless, it is conceivable that PC111, given its unique mechanism of action, could represent a much safer treatment option, possibly sparing or even eliminating the concomitant use of steroids.

While the pathogenesis of SJS/TEN is not fully understood (77), sFasL definitely plays a crucial role in it. Since blocking sFasL halts the disease in preclinical models (86), we expect that PC111 has the potential to save the lives of a huge number of patients suffering from this acute and deadly disorder through its rapid mode of action.

Our development plan for PC111 foresees a common set of IND-enabling studies (CMC and toxicokinetic) for both indications, plus a phase 1–2 study in a relevant subset of patients with either pemphigus or SJS/TEN (to be potentially eligible for accelerated approval), then followed by a confirmatory phase 3 study in each indication.sFasL, the target of PC111, is elevated in sera from pemphigus patients and in the early days of SJS/TEN. Therefore, it will be used in our future studies as a biomarker to predict response to PC111, paving the way to personalized treatment.

Lastly, sFasL is elevated in several other dermatological and non-dermatological conditions, although there is little evidence of its mechanistic involvement in them (90). The availability of reliable models of these diseases will allow the discovery of additional indications for PC111, to be tested in our proprietary humanized FasL mouse model.

The concept of 'disease modification' in dermatology has recently emerged, mostly in relation to chronic inflammatory skin conditions (3). In reality, any therapy that prevents the progression of a disease by impacting on its pathomechanisms and natural course, thus leading to a complete clinical response, could be a potential disease modifier. PC111 could be such a potential disease-modifying drug both in pemphigus and SJS/TEN, by allowing a long-term remission of the disease in the former and by preventing its further progression in the latter.

Ethical approval

The animal study protocol was approved by the Animal Welfare Committee of the University of Modena and Reggio Emilia and carried out in accordance with the Italian Institute of Health guidelines. The protocol was approved by the Italian Ministry of Health (Study code: 406/2015-PR).

Authors contributions

Roberta Lotti: Conceptualization, Data curation, Writing- Original draft preparation. Antonino Amato: Conceptualization, Methodology, Writing- Original draft preparation. Brydon Bennett: Conceptualization, Writing- Original draft preparation. Tommaso Zanocco-Marani: Data curation, Supervision. Alessandra Marconi: Conceptualization, Methodology, Supervision. Carlo Pincelli: Conceptualization, Supervision, Writing- Original draft preparation.

Disclosure statement

TZM has no conflicts of interests to disclose. RL, BB are consultants and shareholders of PinCell srl. AM and CP are co-founders and shareholders of PinCell srl. AA is an employee and shareholder of PinCell srl.

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Data availability statement

Data supporting the findings of this study is available from the corresponding author upon request.

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