Pemphigus and Pemphigoid: From Disease Mechanisms to Druggable Pathways

Christoph T. Ellebrecht[1], Damian Maseda[1] and Aimee S. Payne[1]

Pemphigus and pemphigoid are paradigms for understanding the mechanisms of antibody-mediated autoimmune disease in humans. In pemphigus, IgG4-predominant autoantibodies cause intraepidermal blistering by direct interference with desmoglein interactions and subsequent disruption of desmosomes and signaling pathways. In pemphigoid, IgG1, IgG4, and IgE autoantibodies against basement membrane zone antigens directly interfere with hemidesmosomal adhesion, activating complement and Fc receptor–mediated effector pathways. Unraveling disease mechanisms in pemphigus and pemphigoid has identified numerous opportunities for clinical trials, which hold promise to identify safer and more effective therapies for these potentially life-threatening diseases.

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Introduction

In 1965, Walter Lever published his iconic monograph on pemphigus and pemphigoid (Lever, 1965) discussing why pemphigoid is a distinct disease entity from pemphigus, theories on disease etiology, and groundbreaking success using corticosteroids to treat these highly lethal diseases. In the last half century, our understanding of disease mechanisms in pemphigus and pemphigoid has evolved substantially, although corticosteroids remain the cornerstone of therapy for both diseases. This review will summarize research on disease pathways and clinical trials in pemphigus and pemphigoid.

Pemphigus

Pemphigus is a group of rare, potentially life-threatening diseases that clinically present with flaccid blisters and erosions. The microscopic hallmark of pemphigus is acantholysis or loss of keratinocyte (KC) intercellular adhesion, accompanied by autoantibody binding to the KC cell surface. Autoantibodies target the desmosomal adhesion molecule desmoglein (DSG) 3 in mucosal-dominant pemphigus vulgaris (PV) and target DSG3 plus DSG1 in mucocutaneous PV, causing suprabasal blisters, whereas superficial skin blisters are caused by DSG1 autoantibodies in pemphigus foliaceus (PF) (Kasperkiewicz et al., 2017). Rare atypical PV variants may show desmocollin (DSC) 3 autoantibodies, and autoantibodies targeting other autoantigens can synergistically impair epithelial adhesion, but only DSG3 and DSG1 autoantibodies provide evidence supporting their necessity and sufficiency for causing the specific disease manifestations of PV and PF, respectively (Spindler et al., 2018).

In the consensus model for pemphigus pathophysiology (summarized in Figure 1), DSG autoantibodies bind to DSG3 and/or DSG1, which disrupts KC adhesion through the steric hindrance of DSG interactions (explaining the Nikolsky sign, in which blisters can be induced in normal-appearing skin by shear force), impairment of desmosome assembly and disassembly leading to DSG-depleted desmosomes, and the dysregulation of KC signaling pathways that augment skin blistering (Spindler et al., 2018). Unlike pemphigoid, blister formation in pemphigus is not dependent on complement or Fc-effector functions (Anhalt et al., 1986; Mascaró et al., 1997; Rock et al., 1990). Accordingly, research in pemphigus has focused on characterizing anti-DSG B cells and antibodies as well as signaling pathways that modulate the pathogenic effects of autoantibodies.

Autoimmune B cells. Numerous mAbs specific for DSG3 and/or DSG1 have been cloned from the B cells of patients with PV and PF and mice with experimentally induced PV (Bhol and Ahmed, 2002; Chen et al., 2017; Cho et al., 2019, 2014; Di Zenzo et al., 2012; Ellebrecht et al., 2018; Ishii et al., 2008; Payne et al., 2005;Qian et al., 2012, 2009; Tsunoda et al., 2003; Yamagami et al., 2008; Yeh et al., 2006). Anti-DSG antibodies are 96–100% sensitive and specific for pemphigus diagnosis and are not found in the serum of healthy individuals (Amagai et al., 1999; Schmidt et al., 2010), although nonpathogenic mAb clones recognizing DSG1 proprotein and polyreactive clones that bind DSG3 by ELISA (but not in human skin) can occur (Cho et al., 2014; Yamagami et al., 2009). Pathogenic mAbs target the extracellular cadherin (EC) 1–4 domains of DSG3 and EC1–2 of DSG1 (Cho et al., 2019, 2014; Di Zenzo et al., 2012; Ishii et al., 2008; Payne et al., 2005); no pemphigus sera target only the EC5 domain (Chan et al., 2010; Ohyama et al., 2012). Nonpathogenic mAbs, which are not sufficient on their own to cause acantholysis, either owing to affinity or targeted epitope, can disrupt KC adhesion when clones targeting multiple EC domains are combined, by inducing DSG clustering and downstream signaling pathways (Kawasaki et al., 2006; Saito et al., 2012; Yoshida et al., 2017).

[1]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence: Aimee S. Payne, Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 421 Curie Boulevard, Philadelphia, Pennsylvania 19104, USA. E-mail: aimee.payne@pennmedicine.upenn.edu

Abbreviations: BMZ, basement membrane zone; BP, bullous pemphigoid; BPDAI, Bullous Pemphigoid Disease Area Index; CAART, chimeric autoantibody receptor T cell; CR, complete remission; DSC, desmocollin; DSG, desmoglein; EBV, Epstein–Barr virus; EC, extracellular cadherin; FDA, Food and Drug Administration; KC, keratinocyte; PDAI, Pemphigus Disease Area Index; PF, pemphigus foliaceus; PV, pemphigus vulgaris; SAE, serious adverse event; Th, T helper type; VH, variable heavy

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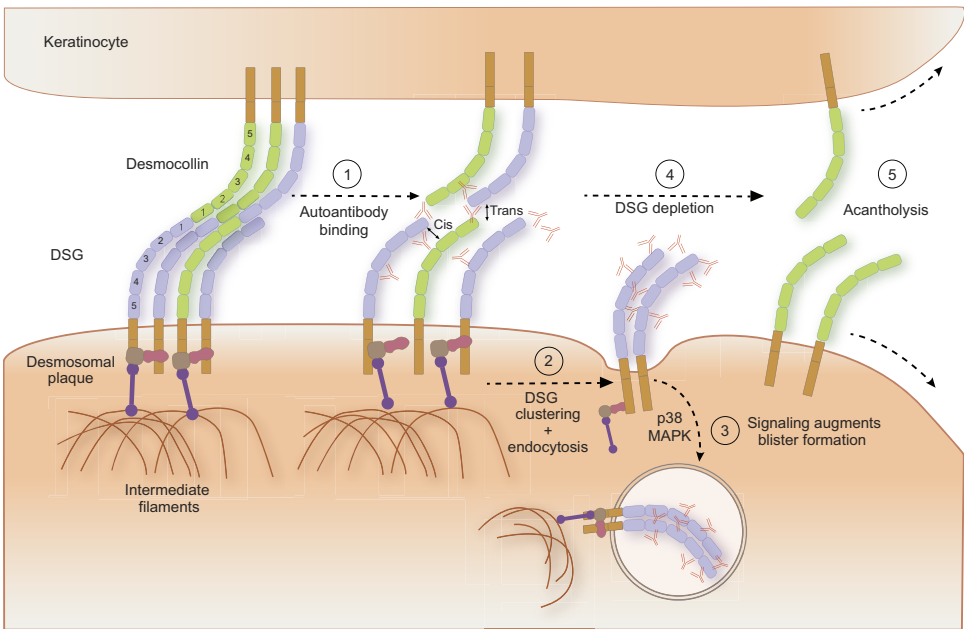

Figure 1. Disease pathways in pemphigus. DSGs interact with cytoplasmic plaque proteins and engage in trans-interactions with desmocollins on neighboring keratinocytes, predominantly through residues in the extracellular cadherin 1 domain, to mediate desmosomal adhesion. (1) Autoantibody binding to DSGs can directly interfere with *cis*- or *trans*-adhesive interactions, weakening desmosomal adhesion. (2) DSG clusters in response to pemphigus IgG binding and internalizes in a p38–MAPK–dependent process. (3) DSG trafficking is most directly regulated by p38–MAPK and protein kinase C; other signaling pathways may synergize to augment blister formation. (4) DSG clustering and endocytosis impair desmosome assembly and promote disassembly, leading to DSG-depleted desmosomes, weakened desmosomal adhesion, and acantholysis (5). DSG, desmoglein. *Illustration assistance provided by Jan Ruvido Stebbins, Ruvido Medical Illustration, Dexter, MI.*

Nonpathogenic antibodies are thought to underlie elevated anti-DSG titers in patients without clinical evidence of disease activity (Cho et al., 2019; Kamiya et al., 2013).

Distinct antibody gene usage patterns in pemphigus have been reported. Anti-DSG1 B-cell clones using variable heavy (VH) chain *VH3-23/3-30* genes are enriched in patients with endemic PF (Qian et al., 2009). In PV, VH1-46 anti-DSG3 B cells are commonly observed (Chen et al., 2017; Cho et al., 2014), and some do not require mutations to bind DSG3, suggesting that naïve VH1-46 B cells may be prone to DSG3 autoreactivity. However, B cells using other VH chain genes require somatic mutations for DSG3 binding (Cho et al., 2019, 2014; Di Zenzo et al., 2012), indicating that most DSG3-reactive B cells arise from affinity maturation. Another distinctive immunologic feature of pemphigus is the predominance of IgG4 autoantibodies (Funakoshi et al., 2012; Futei et al., 2001). Because PV often starts in the mucosa, anti-DSG3 autoreactivity could arise in IgA B cells, which are predominant in mucosal lymphoid tissues. However, lineage-tracing experiments show that anti-DSG3 IgG4 B cells are clonally distinct from IgA and IgG1 B cells and that DSG3-reactive IgA, which is more likely to target nonpathogenic epitopes, may instead develop from sequential class switch from IgG1 B cells (Ellebrecht et al., 2018).

Interestingly, anti-DSG antibodies cross-react with foreign antigens. Anti-DSG1 antibodies from patients with endemic PF can bind salivary antigen LJM11 from the sand fly vector of leishmaniasis (Qian et al., 2012), and DSG3-reactive mAbs can recognize walnut allergen Jug r 2 (Lin et al., 2019), despite the lack of antigen homology. VH1-46 mAbs cross-reactive to DSG3 and rotavirus capsid protein have been identified that cause KC acantholysis and also inhibit rotavirus infectivity (Cho et al., 2016), but such clones are rare, reflecting the distinct somatic mutations that favor DSG3 versus VP6 binding. These findings suggest that in predisposed hosts expressing HLA-susceptibility alleles that favor DSG self-peptide presentation (Wucherpfennig et al., 1995), DSG cross-reactive B cells generated in response to external stimuli may contribute to pemphigus development.

KC adhesion pathways. Research has elucidated the signaling pathways that bolster KC adhesion (Sajda and Sinha, 2018; Spindler and Waschke, 2014). MAPK is a key regulator of DSG endocytosis, although p38–MAPK pathway inhibition in mouse and human epithelial models showed mixed results (Berkowitz et al., 2006; Egu et al., 2020; Mao et al., 2014). A clinical trial of a p38–MAPK inhibitor in PV (NCT00606749) was terminated owing to dose-limiting hepatotoxicity before therapeutic efficacy could be observed. Corticosteroids upregulate DSG expression through the mTOR/signal transducer and activator of transcription 3 axis (Mao et al., 2017; Nguyen et al., 2004), which explains the rapid as well as the topical therapeutic effect of corticosteroids in pemphigus. Overall, signaling inhibition provides an important adjunct to pemphigus therapy but may be insufficient to overcome pathogenicity by high-titer autoantibodies.

Circulating autoantibodies. Although clinical trials have yielded mixed results, plasmapheresis may cause faster clinical improvement and serum autoantibody reductions

than standard-care therapy alone (Guillaume et al., 1993; Tan-Lim and Bystryn, 1990). Intravenous Ig, which increases autoantibody catabolism by saturating FcRn and inhibits Fc-mediated inflammation and antigen presentation (Gelfand, 2012; Li et al., 2005), significantly reduces autoantibody titers and treatment failure in patients with pemphigus receiving up to 20 mg/day prednisolone, supporting its therapeutic efficacy (Amagai et al., 2009). Recently, anti-FcRn mAbs have entered clinical trials (Blumberg et al., 2019; Ulrichts et al., 2018). A total of 5 weekly doses of SYNT001/ALXN1830 (NCT03075904) caused a 46% reduction in Pemphigus Disease Area Index (PDAI) score and 57% reduction in mean IgG levels but only 9–20% reduction in anti-DSG1/DSG3 antibody titers at week 16 (potentially owing to nonlinearity of the DSG ELISA vs. new production or redistribution of tissue autoantibodies). Efgartigimod as an adjunct to up to 0.5 mg/kg/day corticosteroids (NCT04598451) reduced both total IgG4 and anti-DSG IgG levels by approximately 50–60% and mean PDAI score by nearly 90% when dosed at least bimonthly through week 16 (Goebeler, 2020), allowing steroid taper and clinical remission in 7 of 15 patients. A phase 3 trial of subcutaneous efgartigimod in pemphigus is currently recruiting (NCT04598451).

B-cell depletion in pemphigus. Anti-CD20 B-cell depletion with rituximab represents the greatest therapeutic advance in pemphigus since the advent of corticosteroids, resulting in Food and Drug Administration (FDA) approval of rituximab for PV in 2018. In a randomized controlled trial (Joly et al., 2017; see also Chen et al., 2020), 90% of patients receiving first-line maintenance-dose rituximab and corticosteroids achieved complete remission (CR) off steroids for at least 2 months at month 24, compared with 28% of patients treated with high-dose prednisone alone. A subsequent phase 3 trial (NCT02383589; Werth et al., 2021) showed that 40.3% of patients treated with maintenance-dose rituximab and steroids achieved CR off steroids for at least 16 weeks by week 52, compared with 9.5% of patients treated with mycophenolate mofetil and steroids. Serious infections occurred in 8–9% of rituximab-treated patients, compared with 3% treated with high-dose prednisone alone (Rituxan, 2020).

With first-line rituximab plus maintenance infusions, anti-DSG3 antibody titers fall to the undetectable range, indicating that CD20-negative long-lived plasma cells are not a significant autoantibody-secreting cell population in pemphigus. Incomplete B-cell depletion is thought to mediate disease relapse because identical DSG3-reactive B-cell clones are found at initial disease presentation and during disease relapse but are undetectable in long-term remission (Hammers et al., 2015). In addition, B-cell spectratype analysis indicates persistent oligoclonal B-cell expansions during active disease and incomplete remission, which normalize in patients achieving long-term remission (Mouquet et al., 2008). Rituximab does not fully deplete B cells in secondary lymphoid organs (Leandro, 2013) and may poorly penetrate the skin, where lymphoid aggregates containing expanded B-cell clones have been described in patients with pemphigus (Zhou et al., 2020). Other rituximab resistance factors may include genetic defects impairing antibody-dependent cellular cytotoxicity (Weng and Levy, 2003), inhibitory anti-drug antibodies (Lunardon and Payne, 2012), and CD20 downregulation (Tsai et al., 2012). Some resistance mechanisms could be overcome with a higher rituximab dose; accordingly, lymphoma-dose rituximab results in significantly improved responses compared with PV dose (Kushner et al., 2019). Collectively, the data indicate that deeper B-cell depletion is associated with better clinical outcomes.

Novel B-cell targeting agents. Ianalumab (VAY736), a mAb targeting the BAFF-R, causes depletion of late transitional through memory B cells. A randomized controlled trial of ianalumab (NCT01930175) showed a 73% decrease in mean PDAI score at week 12 in seven patients with pemphigus compared with placebo-treated controls. No further clinical development in pemphigus is planned.

Rilzabrutinib (PRN1008) is a Bruton tyrosine kinase inhibitor that impairs plasma cell differentiation and antibody production without depleting B cells. In a phase 2b study (NCT02704429), 10 (67%) of 15 patients with PV showed clear or near-clear skin, and 40% achieved CR after 24 weeks of rilzabrutinib as an adjunct to up to 0.5 mg/kg/day of corticosteroids (Murrell et al., 2020). A phase 3 trial of rilzabrutinib in pemphigus recently completed recruitment (NCT03762265), but failed to meet its primary endpoint of demonstrating superiority to placebo in inducing complete remission with minimal doses of corticosteroids (≤10/mg day), assessed from weeks 29 to 37.

The ideal approach to pemphigus therapy would be to durably deplete only the disease-causing anti-DSG B cells, sparing normal B cells that provide immune protection. On the basis of an FDA-approved chimeric antigen receptor technology (tisagenlecleucel) that can induce lasting remission of B-cell cancers (Maude et al., 2018; Schuster et al., 2019), a precision cellular immunotherapy known as DSG3 chimeric autoantibody receptor T (CAART) cells was developed. Patient T cells are engineered to express a chimeric autoantibody receptor consisting of a DSG3 EC1–4 ectodomain, which comprises all known pathogenic PV autoantibody epitopes, linked to CD137–CD3ζ activation and costimulatory domains (Ellebrecht et al., 2016; Lee et al., 2020). DSG3-CAART is designed to specifically deplete anti-DSG3 B cells and simultaneously produce memory CAART cells that can persist long-term, potentially providing lasting protection against anti-DSG3 B-cell recurrence. A phase 1 trial of DSG3 CAART in mucosal-dominant PV is currently recruiting (NCT04422912).

Pemphigoid

The term pemphigoid refers to a group of subepidermal autoimmune bullous diseases caused by autoantibody binding to epithelial basement membrane zone (BMZ) proteins, resulting in tense bullae and/or urticarial lesions. Diseases (and their associated autoantigens) include bullous pemphigoid (BP) (BP180 and BP230), epidermolysis bullosa acquisita (collagen VII), laminin-332 pemphigoid, mucous membrane pemphigoid (BP180, BP230, and/or α6/β4 integrin), laminin gamma-1 pemphigoid, and linear IgA bullous dermatosis (97/120-kD proteolytic fragments of BP180).

Several excellent previous reviews have discussed the pathophysiology of pemphigoid, primarily focusing on mouse models and human translational studies (Bieber et al., 2021; Dainichi et al., 2017; Edwards et al., 2019; Hammers

and Stanley, 2020, 2016; Messingham et al., 2019). Almost all patients with BP show antibodies against the BP180-NC16A domain and/or BP230, although disease activity correlates with epitopes throughout the BP180 ectodomain (Di Zenzo et al., 2008; Yoshida et al., 2006; Zillikens et al., 1997). Collectively, the published data support a heterogeneous model for disease determined by the relative proportion of IgG1, IgG4, and IgE autoantibodies within patients, which trigger complement- and Fc-gamma receptor–mediated responses, BP180 internalization and weakened hemidesmosomal adhesion, and FcεR–mediated mast cell and eosinophil effector functions, respectively (summarized in Figure 2). Recent clinical trials have provided insight into druggable pathways in BP and their pathophysiologic relevance in human disease.

Autoimmune B cells. The contribution of the B-cell compartment to pemphigoid has been evaluated through clinical studies of rituximab (Berkani et al., 2019; Cho et al., 2015; Hall et al., 2013; Polansky et al., 2019; Tovanabutra and Payne, 2020). Studies with at least 1-year follow-up have shown CR rates of 41–57% (up to 92% with first-line rituximab), significant steroid-sparing effect, and significant decreases in anti-BP180/BP230 IgG titers, correlating with clinical outcome. Disease relapse may be due to incomplete B-cell depletion, evidenced by lower memory B-cell percentage and higher levels of BAFF, which is upregulated after B-cell depletion, in nonrelapsed versus in relapsed subjects (Berkani et al., 2019; Hall et al., 2013). Compared with pemphigus, a lower proportion of patients with pemphigoid achieve CR off oral therapies after rituximab (12–39%, up to 62% with first-line therapy), whereas 76–92% maintained CR when adjunctive low-dose prednisone or dapsone was continued, potentially reflecting the pathogenic importance of leukocyte effectors not targeted by rituximab. Nevertheless, these studies support a key role for IgG B cells in pemphigoid pathogenesis.

Few studies have investigated the pemphigoid B-cell repertoire. Three Epstein–Barr virus (EBV)-transformed anti-BP230 IgG2 B-cell clones were isolated from a patient with BP (Sugi et al., 1989), but no genetic characterization was performed. B-cell spectratype analysis of four patients with BP identified VH5-predominant gene usage by anti-BP180 B cells during active disease and VH3/VH4 predominance after

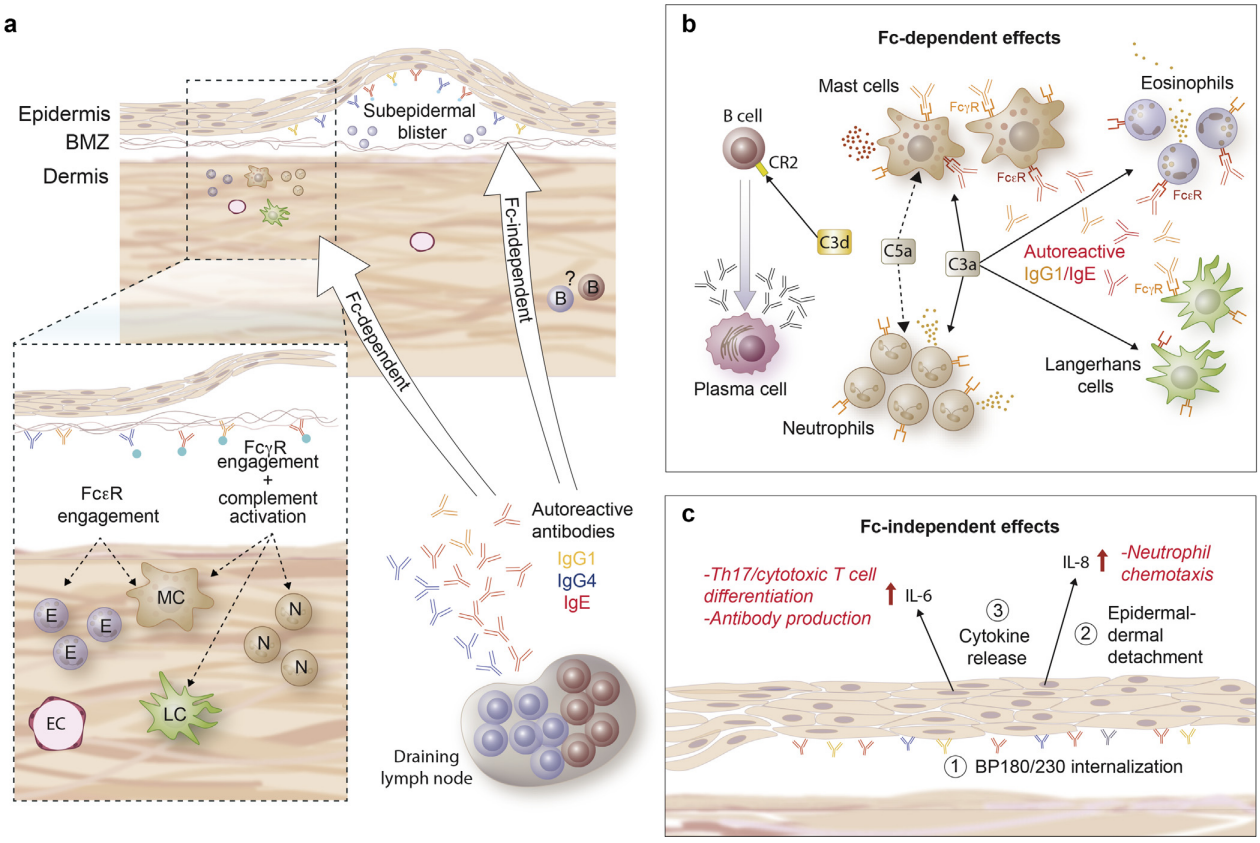

Figure 2. Disease pathways in pemphigoid. (**a**) B cells in skin-draining lymph nodes and possibly dermis secrete IgG1/IgG4/IgE autoantibodies that bind the BMZ, triggering both Fc-independent and Fc-dependent effects. Fc-effector functions include complement activation and FcγR and/or FcεR engagement on Ns, LCs, MCs, Es, and Ecs. (**b**) Fc-dependent effects: C3a/C5a as well as FcγR/FcεR engagement by IgG1/IgE induce chemotaxis, activation, and inflammation. C3d binds B-cell CR2 to promote autoantibody production. (**c**) Fc-independent effects: (1) IgG4 autoantibodies cause internalization of BP180 on basal keratinocytes, leading to dermal–epidermal detachment. (2) Loss of BMZ anchorage activates keratinocyte signaling pathways to induce the secretion of IL-6 (3), which promotes inflammation and antibody secretion by activated B cells as well as IL-8, a neutrophil chemoattractant. BMZ, basement membrane zone; CR2, complement receptor 2; E, eosinophil; Ec, endothelial cell; FcγR, Fc-gamma receptor; LC, Langerhans cell; MC, mast cell; N, neutrophil; Th, T helper type. *Illustration assistance provided by Jan Ruvido Stebbins, Ruvido Medical Illustration, Dexter, MI.*

rituximab therapy (Berkani et al., 2019). Other studies have reported VH1-, VH2-, and VH3-family gene usage by anti-BP180 human mAbs (Li et al., 2010; Wang et al., 2010). One study used phage display to identify two anti-BP180 clones that inhibited binding of polyclonal BP serum IgG and complement activation in human skin and accordingly blocked BP IgG pathogenicity in BP180-humanized mice, supporting the importance of IgG Fc-effector functions in BP (Wang et al., 2010). A second study isolated anti-BP180 IgG1 B-cell clones by EBV immortalization (Li et al., 2010). Passive transfer of 3.B6 IgG1 to BP180-humanized mice caused mast cell and neutrophil chemotaxis, resulting in erythema and blistering similar to phenotypes observed with polyclonal BP IgG. Fc-domain site-directed mutagenesis indicated that complement-dependent cytotoxicity was necessary for disease development in this model, whereas antibody-dependent cellular cytotoxicity played a minor role.

Complement. Studies of pemphigoid skin biopsies have shown that C3d staining has similar sensitivity (74.1%) and specificity (95.8%) to those of direct or indirect immunofluorescence for BP diagnosis, using BP180/230 ELISA as the gold standard (Wang et al., 2020). Complement activation at the BMZ subsequently induces disease pathology in pemphigoid by C3/C5-mediated chemotaxis of mast cells, neutrophils, and/or eosinophils (Bieber et al., 2021; Edwards et al., 2019) and can promote autoantibody production by engagement of B-cell complement receptors by C3d immune complexes (Nikitin et al., 2019).

An anti-C1s antibody, which blocks the classical but not alternative complement pathway, reduces complement fixation by BP IgG on human skin cryosections, supporting the rationale for clinical testing in BP (Kasprick et al, 2018). Humanized anti-C1s mAb (TNT009, now BIVV009) caused no serious adverse events (SAEs) in a phase 1 trial of 64 healthy individuals (Mühlbacher et al., 2017). Four patients with BP were included in the treatment protocol (Derhaschnig et al., 2016), although trial recruitment was suspended, and their outcomes have not been published.

A phase 2 open-label study (NCT04035733) of nomacopan, a dual inhibitor of C5 and leukotriene B4, reported no SAEs related to therapy in nine patients with BP treated with a 6-week subcutaneous daily-dose regimen (Nunn et al., 2021); one patient developed a localized knee infection recorded as an unrelated SAE. Seven patients showed an average of 60% improvement and at least a 4-point drop in the Bullous Pemphigoid Disease Area Index (BPDAI) score, representing a clinically significant difference (Wijayanti et al., 2017). A phase III pivotal study of nomacopan is planned for 2021.

In addition, a phase 2 study of avdoralimab (IPH5401), an anti-C5aR1 mAb, opened in 2020 (NCT04563923). C5aR1-deficient mice are protected from blistering after passive transfer of anti-BP180 IgG, whereas C5aR2 deficiency potentiates disease (Karsten et al., 2018), underlying the rationale for selective targeting of C5aR1.

IgE. Case series indicate that 55–83% of patients with BP, all of whom show elevated serum IgE, achieve complete clearance of skin lesions after a median of 4.4 months therapy with omalizumab, an anti-IgE mAb that blocks FcεR engagement, despite persistent anti-BP180/230 IgG in some patients (Lonowski et al., 2020; Yu et al., 2014). A randomized clinical trial of omalizumab (NCT00472030) was suspended after a patient was hospitalized for congestive heart failure deemed unrelated to therapy. A subsequent randomized trial of the anti-IgE mAb ligelizumab (NCT01688882) showed that by week 12, 6 of 13 patients receiving ligelizumab were clear or almost clear versus 3 of 7 receiving placebo. Only partial trial results have been made public; potential reasons for lack of ligelizumab efficacy may have included the lack of elevated IgE as an inclusion criterion, too short of a treatment period, and/or concomitant use of prednisone, which could obscure a therapeutic effect if used at higher doses.

T helper type 2 axis. T helper type (Th) 2 cytokines and eosinophils, the histologic hallmark of BP skin lesions, have shown promise as potentially effective targets for BP clinical trials. Dupilumab is an anti-IL4Rα mAb that inhibits IL-4 and IL-13 signaling, Th2 differentiation, B-cell class switch, IgE production, and eosinophilic inflammation (Harb and Chatila, 2020). Skin-homing IL-4/IL-13 T cells are elevated in BP (Teraki et al., 2001). A case series reported improvement of bullae and/or pruritus in 12 of 13 patients treated with dupilumab, 7 of whom experienced CR (Abdat et al., 2020). These data support the rationale for an ongoing phase 2/3 study of dupilumab in BP (NCT04206553).

Bertilimumab, an anti–eotaxin-1 mAb that inhibits eosinophil chemotaxis, was administered to nine patients with BP on days 0, 14, and 28 (NCT02226146), resulting in an 81% reduction in BPDAI score and a mean steroid dose reduction from 28 mg to 12 mg by week 12 (Immune Pharmaceuticals, 2018). A pivotal study of bertilimumab in BP was terminated owing to sponsor bankruptcy.

Mepolizumab, an anti–IL-5 mAb approved for the treatment of eosinophilic asthma, was clinically evaluated in BP (Simon et al., 2020). A total of 30 patients were randomized to receive mepolizumab or placebo for 12 weeks, plus 0.5 mg/kg prednisolone until the achievement of disease control, followed by prednisolone dose reduction by 20% every 2 weeks. At week 16, there was no difference in the rate of patients who achieved disease control or were relapse free, despite significantly lower blood eosinophils in mepolizumab-treated patients. Mepolizumab-treated patients required less prednisolone (258 mg vs. 445 mg), reflecting an earlier time to disease control, but differences were not significant. This could potentially be due to small study size, short treatment period, insufficient neutralization of soluble IL-5 or reduction in tissue eosinophils, and/or concomitant use of a highly effective dose of prednisolone, which may have obscured mepolizumab's potential therapeutic effects. Benralizumab, a mAb targeting the IL-5Rα expressed on eosinophils and basophils, is also entering clinical trials for BP (NCT04612790). Targeting the IL-5Rα instead of IL-5 offers the advantage of causing eosinophil and mast cell lysis in addition to IL-5/IL-5Rα blockade and is theoretically more effective in conditions with high circulating IL-5 levels, although shedding of soluble IL-5Rα could in part neutralize benralizumab activity.

IL-23/IL-17. Previous studies have shown elevated IL-17/IL-23 in the skin and blood of patients with BP (Chakievska

et al., 2019; Le Jan et al., 2014). IL-17 upregulates matrix metalloproteinase 9 and neutrophil elastase, which are necessary for disease in neutrophil-predominant experimental BP models (Chakievska et al., 2019; Liu et al., 2000, 1998). Ustekinumab, a mAb targeting the IL-12/23 p40 subunit, as well as the IgG1 kappa anti-IL17A mAb secukinumab, have anecdotally induced BP remission (Holtsche et al., 2020; Loget et al., 2017). However, ustekinumab-induced BP has also been reported (Le Guern et al., 2015; Marin et al., 2021; Nakayama et al., 2015). Clinical studies of ustekinumab (NCT04117932) and tildrakizumab (NCT04465292), an anti-IL23 p19 mAb, are currently planned in BP. In a phase 2 study of the IgG4 anti-IL17A mAb ixekizumab (NCT03099538), four patients with BP failed to achieve control of blister formation associated with a rise in mean BPDAI score of 25 at baseline to 39 at week 12. These findings suggest that IL-17A is not a primary driver of pathology in BP, potentially reflecting the eosinophil predominance in human BP, as opposed to the neutrophil-predominant pathology in most mouse pemphigoid models.

Summary

In the last half century, research advances have identified potentially druggable pathways in pemphigus and pemphigoid, and subsequently, clinical trials have further refined our models of disease pathogenesis. B-cell depletion with rituximab in pemphigus can achieve complete but transient disease remission; therapies that more durably or safely deplete pathogenic B cells or antibodies are the focus of ongoing clinical development. Pemphigoid clinical trials are mostly targeting effector pathways triggered by autoantibodies, such as complement and the Th2 axis. Human clinical studies offer exciting promise to continue the synergy of the bench-to-bedside and bedside-to-bench research process to advance our understanding of pemphigus and pemphigoid pathophysiology.

ORCIDs

Christoph T. Ellebrecht: http://orcid.org/0000-0001-7656-0491
Damian Maseda: http://orcid.org/0000-0003-0722-6881
Aimee S. Payne: http://orcid.org/0000-0001-9389-7918

CONFLICT OF INTEREST

ASP reports equity (Cabaletta Bio), patent licensing (Cabaletta Bio, Novartis, Tmunity Therapeutics), grant support (Cabaletta Bio), and consultant fees (Cabaletta Bio, Villaris Therapeutics). CTE reports equity (Cabaletta Bio) and patent licensing (Cabaletta Bio, Novartis, Tmunity Therapeutics). The remaining author states no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CTE, DM, ASP; Visualization: CTE, DM, ASP; Writing - Original Draft Preparation: CTE, DM, ASP; Writing - Review and Editing: CTE, DM, ASP

Disclaimer

The content of this study is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (Bethesda, MD).

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