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# Advances in Immunopathology of Pemphigus Vulgaris: From Autoantibodies to Targeted Therapy

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## Abstract

Pemphigus vulgaris (PV) is a rare but potentially life-threatening autoimmune blistering disorder characterized by circulating IgG autoantibodies that target the desmosomal cadherins desmoglein-3 (Dsg3) and desmoglein-1 (Dsg1). These autoantibodies impair keratinocyte adhesion, leading to loss of cell–cell cohesion (acantholysis) and the formation of painful mucocutaneous erosions. While early models emphasized steric hindrance of desmosomal adhesion as the primary pathogenic mechanism, contemporary research has revealed that PV is a multifactorial disorder involving complex interactions between humoral immunity, T-cell dysregulation, genetic susceptibility and keratinocyte signalling pathways. Autoantibody binding not only blocks adhesion but also activates intracellular signalling cascades, triggers desmoglein internalization and promotes cytoskeletal remodelling, collectively contributing to desmosome destabilization. Advances in immunology have identified key roles for B-cell subsets, follicular helper T cells, regulatory T-cell dysfunction and HLA class II alleles in promoting autoantibody production and loss of tolerance. These mechanistic insights have led to transformative changes in the therapeutic landscape. Rituximab, an anti-CD20 monoclonal antibody, has become a standard first-line therapy, offering superior remission rates compared with conventional immunosuppression. More recent innovations, including neonatal Fc receptor (FcRn) inhibitors, Bruton's tyrosine kinase (BTK) inhibitors and antigen-specific approaches such as chimeric autoantibody receptor T (CAAR-T) cells, aim to provide targeted, durable disease control with reduced systemic toxicity. This review synthesizes current knowledge on the immunopathology of PV and highlights how mechanistic advances have driven the development of next-generation therapies, ultimately moving the field toward precision and potentially antigen-specific treatment strategies.

**Keywords:** Acantholysis Mechanisms, Autoimmune Blistering Diseases, B-Cell Targeted Therapy, CAR-T Cell Therapy, Desmoglein Autoantibodies, FcRn Inhibition.

## Introduction

Pemphigus vulgaris (PV) is a rare, severe and potentially life-threatening autoimmune blistering disorder of the skin and mucous membranes, historically associated with mortality rates exceeding 75% before the introduction of systemic corticosteroids in the mid-20th century. Although advances in immunosuppressive therapy have dramatically reduced mortality, PV continues to impose a substantial disease burden due to chronic mucosal erosions, susceptibility to secondary infections, nutritional compromise and the long-term toxicities of prolonged corticosteroid use (1, 2). As one of the most extensively studied organ-specific autoimmune diseases, PV has provided a valuable model for understanding mechanisms of autoantibody mediated tissue injury. The illness also emphasises the fine balance needed to preserve immunological tolerance and epithelial integrity, which makes it a crucial point of reference for researching other autoimmune blistering illnesses. The therapy of PV is made more difficult by its chronic relapsing nature, which frequently calls for extended surveillance and many therapeutic interventions. Pain, difficulties eating and visible skin lesions often significantly impact patients' quality of life, highlighting the need for safer and more effective long-term treatments.

The immunopathologic hallmark of PV is the presence of pathogenic IgG autoantibodies directed primarily against the desmosomal cadherins desmoglein-3 (Dsg3) and, in many cases, desmoglein-1 (Dsg1) (2, 3). These desmosomal proteins are indispensable for maintaining keratinocyte–keratinocyte adhesion in stratified epithelial tissues. Classic studies in neonatal mouse models demonstrated that passive transfer of patient IgG induces reproducible intraepider-



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mal blistering, firmly establishing that autoantibodies are both necessary and sufficient to cause disease (4). Early pathogenic models focused largely on the concept of steric hindrance, whereby autoantibodies directly interfere with Dsg-mediated adhesion. This antibody-centric view dominated the field for decades. However, major advances in molecular immunology and epithelial cell biology have reshaped the understanding of PV pathogenesis. It is now clear that the disease involves a multifaceted interplay of humoral and cellular autoimmune mechanisms, keratinocyte signaling pathways and structural alterations within desmosomes. Recent studies show that autoantibody binding triggers signaling cascades involving p38 MAPK, EGFR/Src and Rho family pathways, contributing to cytoskeletal reorganization and desmosome disassembly (5-7). Autoantibody-induced endocytosis and depletion of desmogleins from the keratinocyte surface further weaken intercellular adhesion (8, 9). Beyond antibodies, B-cell dysregulation, follicular helper T cell support and deficiencies in regulatory T cell function drive the chronic production and maturation of autoreactive clones (9-11). Genetic predisposition and related class II alleles play a central role by shaping antigen presentation and loss of tolerance to desmoglein peptides (11). Environmental factors have also been identified as triggers that may cause or worsen disease in genetically sensitive individuals, including medicines, infections and potentially stress. Additionally, epitope spreading has been seen as the disease progresses, indicating that the autoimmune response may expand with time and contribute to the severity and longevity of the illness.

The immunologic and mechanistic insights have directly influenced the evolution of therapeutic strategies. Traditional therapies include cortico-steroids combined with broad immune-suppressants such as azathioprine or mycophenolate mofetil. They are effective but non-specific, often resulting in substantial cumulative toxicity (1, 2). The introduction of rituximab, a monoclonal antibody targeting CD20+ B cells, marked a major paradigm shift. Clinical trials demonstrated that rituximab induces higher rates of durable remission and steroid sparing benefits compared with conven-tional therapy, leading to its adoption as a first line treatment in many guidelines (12, 13). Building upon deeper understanding of IgG behavior and B-cell biology, several new targeted therapies have emerged. FcRn inhibitors such as efgartigimod and rozanolixizumab accelerate pathogenic IgG clearance, providing rapid reductions in autoantibody levels and early clinical improvement in trials (14-17). Bruton's tyrosine kinase (BTK) inhibitors modulate B-cell receptor signaling and show promise as orally administered, targeted immunomodulators (18, 19). Most notably, advances in precision immunotherapy have led to the development of chimeric autoantibody receptor T (CAAR-T) cells, exemplified by DSG3-CAR-T, which are designed to specifically eliminate anti-Dsg3 B cells while sparing the rest of the immune repertoire, an approach with the potential for highly durable, antigen-specific tolerance (20-22). The growing therapeutic landscape is reflected in the exploration of further experimental techniques, such as cytokine regulation and plasma cell-targeted therapy.

Given the rapid expansion of molecular insights and therapeutic innovations, an updated synthesis of the immunopathology of PV is essential. A mechanistically integrated view, linking autoantibody generation, T and B cell dysregu-lation, genetic susceptibility, keratinocyte signaling and desmosomal biology, provides a conceptual foundation for understanding current treatments and for anticipating future advances. As the field transitions from broad immune-suppression to precision targeted and antigen specific therapies, a comprehensive analysis of these developments is critical for clinicians, researchers and translational scientists working to improve outcomes for patients with pemphigus vulgaris. In order to translate these scientific advancements into standard clinical practice and ultimately aim for safer, more effective and perhaps curative medicines, interdisciplinary collaboration and well-designed clinical trials will be essential.

## Methodology

This review was conducted using a structured, narrative-based methodology designed to integrate current evidence on the immune-pathology and evolving therapeutic landscape of pemphigus vulgaris (PV). The approach combined

comprehensive database searches, critical appraisal of peer reviewed literature and selective inclusion of high-quality clinical evidence, mechanistic studies and authoritative reviews.

A systematic search was performed using PubMed**,** ScienceDirect**,** Google Scholar and ClinicalTrials.gov for literature published between 2000 and 2025, reflecting the period during which major advances in PV immunopathology and targeted therapies were made. Search terms included "pemphigus vulgaris", "desmoglein," "autoantibodies", "acantholysis", "B-cell dysregulation", "rituximab pemphigus", "FcRn inhibition", "BTK inhibitor pemphigus", "CAAR-T pemphigus" and "DSG3 autoimmunity". Additional terms were combined using Boolean operators to ensure comprehensive retrieval of relevant material. Key foundational references, including early immunopathology studies and seminal clinical trials, were identified and prioritized (2-4, 6, 12).

Inclusion criteria emphasized peer-reviewed clinical trials**,** such as those evaluating rituximab, FcRn inhibitors and BTK inhibitors; mechanistic and translational immunology studies, particularly those detailing desmosomal biology, signaling pathways and autoantibody pathogenicity; genetic and immunogenetic studies involving HLA associations and T-cell epitope mapping; foundational reviews and textbooks offering validated descriptions of disease mechanisms and diagnostic principles; clinical practice guidelines and consensus statements**,** including those defining standardized response criteria and outcome measures; ongoing or completed clinical trial data, including registries and industry reports on emerging therapies such as DSG3-CAART (21-24).

Articles not available in English, case reports without mechanistic relevance and studies with inadequate methodology or insufficient data quality were excluded. To ensure accuracy and currency, each selected paper was reviewed in full, with emphasis on mechanistic insights, experimental rigor and clinical relevance.

The references used to inform this review represent a diverse body of evidence: randomized controlled trials (RCTs) and long-term cohort studies for rituximab; Phase I–III studies for FcRn and BTK inhibitors; preclinical and early clinical development of CAAR-T cells; as well as classical immunopathologic descriptions and updated molecular models of keratinocyte signaling and desmosome regulation (17-22).

This methodology allowed synthesis of current knowledge into an integrated thematic review linking fundamental immunopathology to therapeutic innovation. While not a formal systematic review, it adheres to rigorous standards for scientific narrative reviews and incorporates high-level evidence where available.

# Results

## Overview of Pemphigus Vulgaris

### Clinical Presentation and Epidemiology

PV primarily affects adults (peak 4th–6th decades) and is characterized by painful mucosal erosions (especially oral) and flaccid cutaneous blisters that easily rupture. The worldwide incidence varies by geography and ethnicity, with higher rates reported in certain populations (e.g., Jewish, Middle Eastern and South Asian groups). Mortality has decreased substantially with modern therapy but disease burden remains high because of infections, treatment-related adverse effects and impaired quality of life (1).

### Diagnostic Hallmarks

Diagnosis of PV relies on a triad:

a) Characteristic clinical findings,
b) Histology showing suprabasal acantholysis and
c) Immunopathology – direct immunofluorescence (DIF) of perilesional skin demonstrating intercellular IgG and C3 deposition in the epidermis.
d) Serologic testing (indirect immunofluorescence,
e) ELISA for anti-Dsg1 and anti-Dsg3 supports diagnosis and monitoring; titers correlate variably with disease activity (2).

## Immunopathology of Pemphigus Vulgaris

### Autoantibodies: Targets, Subclasses and Pathogenic Mechanisms

### Desmogleins as Principal Autoantigens

Understanding PV immunopathology requires integrating humoral autoimmunity (autoantibodies), cellular immunity (T-cell help, regulatory dysfunction), genetics and keratinocyte biology.

The desmosomal cadherins Dsg3 and Dsg1 are the principal autoantigens in PV and pemphigus

foliaceus (PF). In PV, anti-Dsg3 antibodies predominate and mediate mucosal disease; combined anti-Dsg3 and anti-Dsg1 antibodies cause mucocutaneous disease. The "desmoglein compensation" model explains clinical phenotype by considering the tissue distribution of Dsg isoforms: mucosa predominantly expresses Dsg3 (hence anti-Dsg3 leads to mucosal lesions), whereas epidermis expresses both Dsg1 and Dsg3 (2).

**Fine Specificity and Isotype Matter**

Not all anti-desmoglein antibodies are pathogenic. Pathogenicity depends on epitope specificity (which extracellular domains are targeted) and IgG subclass. For PV, IgG4 is often the dominant subclass among pathogenic antibodies and associates with disease activity; IgG1 and other subclasses can also be present. Antibodies that target adhesive interfaces (e.g., the EC1 domain of Dsg3) more readily disrupt trans-adhesion (2).

**Mechanisms of Acantholysis: Steric Hindrance, Desmoglein Internalization and Signaling**

Several non-exclusive mechanisms explain how autoantibodies cause acantholysis:

a) Steric hindrance / direct inhibition:
   Autoantibodies block Dsg trans-adhesive interactions, directly weakening adhesion.
b) Desmoglein internalization and depletion:
   Antibody binding can trigger endocytosis and degradation of Dsg molecules, reducing cell surface adhesive capacity.
c) Activation of intracellular signaling cascades:
   Autoantibody binding can trigger keratinocyte signaling — p38MAPK, EGFR, Src family kinases and others - that leads to cytoskeletal reorganization, desmosome disassembly and cell detachment. These signaling events amplify loss of adhesion beyond simple antigen-blocking. Recent work has expanded understanding of dynamic desmoglein signaling and its role in keratinocyte biology (3).

**Complement and Fc Receptor Involvement**

Complement activation is variably implicated; complement deposition is not a universal finding in PV DIF. Fc–Fcγ receptor interactions (including engagement of FcRn influencing IgG half-life) and downstream effector mechanisms contribute to antibody pathogenicity and clearance dynamics, motivating therapies that alter IgG handling (e.g., FcRn inhibitors) (3).

**B Cell Biology, Plasmablasts and Long-lived Plasma Cells**

Autoreactive B cells, arising due to failed tolerance checkpoints and T-cell help, differentiate into plasmablasts and plasma cells that secrete pathogenic IgG. Short-lived plasmablasts in blood often correlate with active disease and respond to B-cell depletion therapies like anti-CD20. Long-lived bone marrow plasma cells can be refractory to CD20-targeting and may underpin refractory disease, motivating strategies to target plasma cells (e.g., proteasome inhibitors) or selectively remove circulating pathogenic IgG (plasmapheresis, FcRn blockade) (20).

**T Cell Help, HLA Associations and Tolerance Breakdown**

CD4+ T helper cells are essential for class-switching and affinity maturation of anti-Dsg B cells. Specific HLA class II alleles associate strongly with PV susceptibility in many populations and constrain the repertoire of Dsg peptides presented to T cells; T-cell epitope mapping has identified DR-restricted peptides that stimulate autoreactive T cells. Regulatory T cells (Tregs) and mechanisms of peripheral tolerance are implicated in disease onset and activity (25).

**Genetic and Environmental Modifiers**

Genetics (HLA and non-HLA loci) shape susceptibility; environmental triggers include drugs, viral infections and possibly UV light. Some medications (e.g., penicillamine, captopril) can induce pemphigus-like disease, often through neoantigen/immune alterations (2).

**Molecular and Cellular Pathways in PV-Translational Insights**

Recent translational work has mapped signaling nodes and keratinocyte responses that mediate antibody-induced acantholysis, with important therapeutic implications: p38MAPK and downstream effectors: Activation contributes to cytoskeletal changes; its inhibition reduces blister formation in models. EGFR/Src signaling: These pathways influence desmosomal stability and keratinocyte adhesion; cross-talk with endocytic machinery mediates Dsg internalization. Desmoglein clustering and compensation: Antibody binding changes desmoglein distribution and stability in desmosomes, altering mechanical resilience. Immunoregulatory feedback: Autoantibody presence influences B-cell maturation and

epitope spreading; FcRn modulation can alter IgG persistence and antigen presentation. Recent systematic reviews emphasize the bidirectional signaling role of desmosomal cadherins beyond structural adhesion, linking autoantibody binding to cellular signaling outputs (5). These insights indicate multiple intervention points: blocking pathogenic IgG, removing autoreactive B cells, disrupting B-cell receptor signaling (BTK), interfering with IgG recycling (FcRn) and antigen-specific immune ablation (CAAR-T).

**Diagnostic and Biomarker Advances**

While DIF, ELISA for anti-Dsg1/Dsg3 and IIF remain standards, advances include: Refined epitope mapping and subclass assays to distinguish pathogenic from non-pathogenic antibodies; Cellular assays measuring antibody-induced keratinocyte signaling or internalization as functional correlates of pathogenicity; Monitoring B-cell/plasmablast populations by flow cytometry during therapy (e.g., after rituximab) to guide retreatmen; Use of IgG-FcRn and total IgG measurements in trials of FcRn inhibitors to track pharmacodynamic effect. These biomarkers support individualized therapy and better mechanistic understanding in trials (3).

## Targeted Therapy: From Concept to Clinic

**Anti-CD20 Therapy - Rituximab as a Paradigm Shift**

Historically, high-dose systemic corticosteroids and conventional immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide) were mainstays. The last 15 years have seen a revolution toward targeted approaches informed by PV immunopathology.

Rituximab, a chimeric anti-CD20 monoclonal antibody that depletes mature B cells, has become a first-line therapy for many PV patients and has transformed outcomes. Protocols vary (lymphoma vs rheumatoid arthritis dosing), but randomized data and real-world cohorts show rituximab induces higher rates of sustained remission and steroid sparing compared with conventional therapy. Re-emergence of disease often correlates with B-cell repopulation and recurrence of anti-Dsg antibodies. Long-term follow-up supports durable responses in many patients, though relapses and infections remain concerns. Recent studies have explored lower-dose rituximab regimens with promising efficacy and decreased cost/toxicity (26).

**FcRn Blockade - Accelerating IgG Clearance**

The neonatal Fc receptor (FcRn) rescues IgG from lysosomal degradation and regulates IgG half-life. FcRn antagonists (e.g., efgartigimod, rozanolixizumab) promote IgG catabolism, reducing circulating pathogenic IgG and enabling rapid clinical improvement. Phase II studies of efgartigimod showed early disease control and reductions in total IgG and anti-Dsg titers; however, a Phase III trial did not meet its primary endpoint per corporate reporting, highlighting both promise and the challenges of trial design in pemphigus (heterogeneous disease, background therapies). FcRn blockade remains a mechanistically attractive approach and platform for combination strategies (27).

**BTK Inhibitors — Targeting B Cell Signaling**

Bruton's tyrosine kinase (BTK) is essential for B-cell receptor signaling and plasmablast survival. Oral reversible BTK inhibitors (e.g., rilzabrutinib/PRN1008) have been tested in PV. Rilzabrutinib trials showed tolerability and some signals of efficacy, but primary endpoints in pivotal settings have been challenging to meet; nonetheless, prespecified analyses suggest BTK inhibition remains a biologically plausible strategy. BTK inhibitors might be particularly useful as oral steroid-sparing agents or in combination with B cell depletion (18).

**Antigen Specific Cellular Therapy - DSG3-CAART (CAAR-T)**

A transformative and highly specific strategy is the use of chimeric autoantibody receptor T (CAAR-T) cells engineered to express the autoantigen (e.g., Dsg3) extracellular domains fused to T-cell signaling domains. DSG3-CAART are designed to selectively deplete autoreactive B cells that recognize Dsg3, sparing the rest of the B-cell repertoire. Early phase I/II clinical trials (DesCAARTes and related studies) have explored safety and proof-of-concept; clinical development is ongoing and represents the first antigen-specific immune ablation strategy in PV. The approach mirrors CAR-T success in hematologic malignancies but is tailored for autoimmunity.

**Other Targeted and Adjunctive Strategies**

Proteasome inhibitors (e.g., bortezomib) target plasma cells; used in refractory cases with variable success. Belimumab (anti-BAFF)

modulates B-cell survival; explored in small series. Complement and FcγR modulation: Less central than in other antibody-mediated diseases but remains an area of interest. Tolerogenic vaccines / peptide therapies: Attempt to restore tolerance by presenting Dsg peptides in tolerogenic contexts — early stage. Topical and local approaches: For localized disease or mucosal erosions, adjunctive topical therapy or intralesional approaches may be useful.

Each approach has a distinct rationale based on pathophysiologic nodes (B-cell depletion, IgG clearance, BCR signaling blockade, antigen-specific elimination). Combination strategies (e.g., short-term FcRn inhibition for rapid control plus rituximab for durable suppression) are rational and under exploration (28).

## Clinical Trial Landscape - Selected Highlights

Table 1 summarizes the clinical trials performed till date.

**Table 1:** Summary of Emerging Targeted Therapies against Pemphigus Vulgaris

| Therapy | Evidence Summary | Reference |
|---|---|---|
| Rituximab | Multiple randomized and observational studies demonstrate superiority over conventional therapy for inducing and maintaining remission. Dosing regimens vary and lower-dose protocols are under evaluation. | (26) |
| Efgartigimod (argenx) | Phase II trials demonstrated rapid clinical responses and significant IgG reductions. However, Phase III ADDRESS topline results did not meet the primary endpoint, reflecting challenges in heterogeneous PV populations. Further analyses and combination-therapy studies are ongoing. | (27) |
| Rilzabrutinib | Phase II/III programs showed acceptable tolerability. Primary efficacy endpoints have been difficult to meet, but prespecified sensitivity analyses reveal signals of clinical activity. BTK inhibitors remain promising as oral immunomodulators. | (18) |
| DSG3-CAART (CAAR-T) | Early-phase clinical trials (DesCAARTes™) are evaluating safety, feasibility and initial efficacy of antigen-specific T-cell therapy. Translational immunologic readouts and longer-term results are anticipated. | (28) |

## Practical Therapeutic Considerations and Treatment Algorithms

Modern management of moderate-to-severe PV increasingly favors early rituximab combined with a short-course corticosteroid as a steroid-sparing induction in many centers. For refractory or relapsing disease, options include repeat rituximab, FcRn inhibitors, BTK inhibitors, proteasome inhibitors, or enrollment into trials of CAAR-T. Treatment must be individualized considering disease severity, comorbidities, infection risk, pregnancy considerations and access/cost. Monitoring includes clinical assessment, anti-Dsg ELISA titers (with caution not to overinterpret single values), B-cell counts post-rituximab and vigilance for adverse events (infection, infusion reactions, reactivation of latent infections).

## Challenges, Unmet Needs and Future Directions

### Heterogeneity and Trial Design

PV is heterogeneous in clinical pattern, autoantibody profiles and natural history. This heterogeneity complicates trial endpoints and statistical power. Standardized definitions (e.g., Pemphigus Disease Area Index [PDAI]) and steroid-sparing endpoints improve consistency, but careful trial design remains essential (27).

### Targeting Long-Lived Plasma Cells

Because bone marrow plasma cells may persist after anti-CD20, strategies to eliminate long-lived plasma cells (e.g., proteasome inhibition, anti-CD38) or to tolerize the immune system permanently are active areas of research.

### Antigen Specific Immune Therapies

DSG3-CAART and related approaches represent a paradigm shift: antigen-specific removal of

autoreactive B cells could minimize global immunosuppression and infection risk. Issues under study include durability, safety (on-target/off-target) and manufacturing/logistical aspects (29).

**Combination and Sequencing Strategies**

Rational combinations—rapid IgG removal (FcRn blockade or plasmapheresis) for early control, followed by B-cell depletion for durable remission, possibly topped up with CAAR-T for refractory clones—are conceptually attractive but require systematic evaluation.

**Biomarkers to Predict Response and Personalize Therapy**

Better biomarkers (T-cell signatures, B-cell clonality, plasma cell reservoirs, epitope specificity) could guide choice and timing of therapy and predict relapse risk.

## Discussion

Advances in the understanding of pemphigus vulgaris (PV) highlight the dynamic interplay between autoantibodies, B and T cell dysregulation and keratinocyte signaling abnormalities. Although desmoglein-directed IgG remains the central pathogenic factor, current evidence demonstrates that intracellular signaling pathways, desmoglein internalization and genetic susceptibility significantly modify disease expression and therapeutic response. Targeted treatments, particularly rituximab, FcRn inhibitors, BTK inhibitors and CAAR-T cell therapy, illustrate how mechanistic discoveries translate directly into clinical innovation. However, challenges remain, including heterogeneity in treatment response, persistence of long-lived plasma cells and limited access to advanced biologics in many regions. Further research is needed to refine biomarkers, optimize therapy sequencing and develop safe, antigen-specific strategies capable of inducing durable immune tolerance. As understanding deepens, PV management is expected to shift from broad immunosuppression toward precision, mechanism-based interventions.

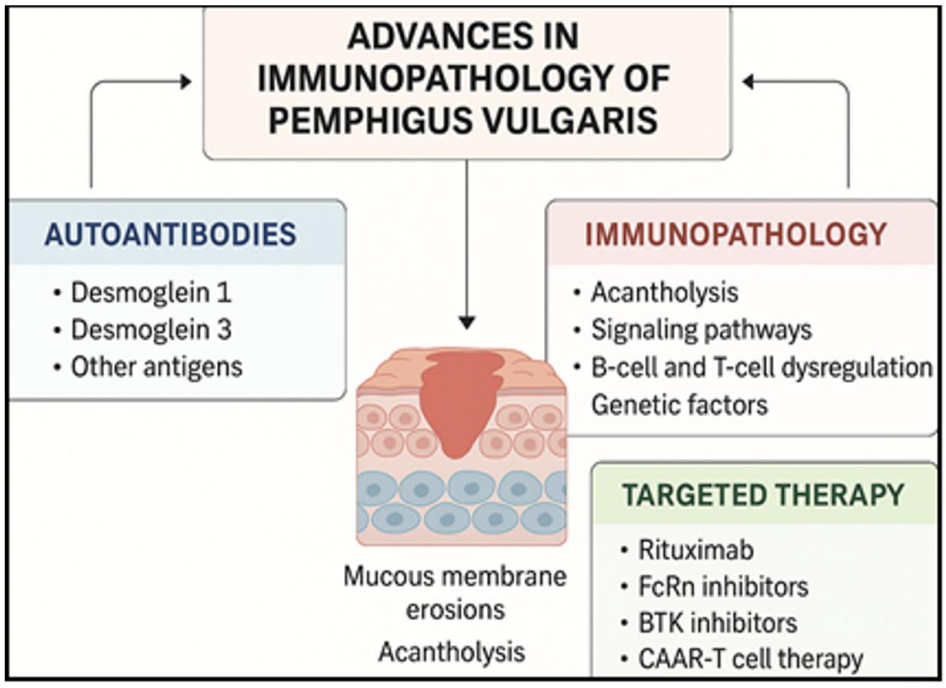


**Figure 1:** Overview of Advances in the Immunopathology and Targeted Treatment of Pemphigus Vulgaris

## Conclusion

As summarized in Figure 1, pemphigus vulgaris exemplifies how mechanistic insights into autoimmunity can translate into precision therapies. From the central discovery that pathogenic IgG targets desmogleins, research has expanded to a nuanced understanding of antibody fine specificity, keratinocyte signaling, B and T cell dynamics and immune homeostasis. These advances have already delivered tangible clinical gains: rituximab transformed outcomes; FcRn

antagonists demonstrated proof-of-concept for rapid IgG removal; BTK inhibitors offered oral targeted suppression; and CAAR-T approaches promise antigen-specific immune ablation. Yet challenges remain - heterogeneity, long-lived plasma cells, trial design complexities and equitable access and solving them will require integrative translational efforts, robust biomarkers and innovative trial designs. The future of PV therapy looks to be precision-driven: targeted, rationally combined and aimed at durable tolerance rather than indefinite global immunosuppression. Crucially, the necessity for individualised treatment approaches is highlighted by interpatient diversity in autoantibody profiles, treatment response and disease severity. This heterogeneity is starting to be revealed at a never-before-seen level because to developments in high-throughput technologies like proteomics and single-cell sequencing. The discovery of predictive biomarkers that direct therapy choice and maximise intervention time may be made possible by these technologies. Combination strategies that target several disease pathways at once may also increase efficacy while reducing toxicity. Maintaining remission will probably depend heavily on long-term illness surveillance and flexible treatment approaches. In the end, controlling PV and achieving a long-lasting, treatment-free remission are both possible with the integration of mechanistic knowledge and clinical innovation.

## Abbreviations

BTK: Bruton's tyrosine kinase, CAAR-T: Chimeric autoantibody receptor T (CAAR-T), Dsg: Desmoglein, FcRn: Neonatal Fc receptor, PF: Pemphigus foliaceus, PV: Pemphigus vulgaris, RCTs: Randomized controlled trials.

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## Author Contributions

All the authors contributed equally.

## Conflict of Interest

The authors share no conflict of interest.

## Data Availability

The data are available from the corresponding author upon a reasonable request.

## Declaration of Generative AI and AI-Assisted Technologies

The authors used generative AI to assist with language editing and grammatical refinement. The authors critically reviewed and edited the output and maintain complete accountability for the originality and integrity of the published work.

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