

Recent Patents in *Pemphigus* Research, Prophylaxis, Diagnosis and Treatment in USA (1988-2006)

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Abstract: *Pemphigus* is an autoimmune blistering disease which is characterized histologically by intraepidermal blisters due to separation of epidermal cell-cell contacts, and immunopathologically by circulating IgG type autoantibodies directed against the desmosomes, which is the cell-cell attachment device in the epidermis. This review briefly summarizes current concepts of conventional diagnosis and treatment of pemphigus, and then focuses on recent US patents related to *Pemphigus* research, prophylaxis, and diagnosis and treatment from 1988 to 2006. As a result, possible new therapeutic approaches, prophylaxis, diagnostic procedures, or experimental models for the *Pemphigus* have been disclosed.

Keywords: Compound, DNA sequence, mapping, plasmapheresis, HLA typing, DELPHION.

INTRODUCTION

Pemphigus is an autoimmune blistering disease characterized clinically by erosion or flaccid superficial bullae in the mucous membrane and/or skin, histopathologically by intraepidermal blisters called acantholysis (separation of cell-cell contacts) in the epidermal keratinocytes, and immunopathologically by circulating IgG-type autoantibodies directed against desmosomes, the cell-cell attachment devices of keratinocytes [1]. *Pemphigus* is divided into four major types: *Pemphigus vulgaris*, foliaceus, paraneoplastic, and IgA *Pemphigus*. Furthermore, variants of the first two types are well-known; *Pemphigus vegetans* (severe variant of *Pemphigus vulgaris*) and *Pemphigus erythematousus* (mild variant of *Pemphigus foliaceus*) [1]. In *Pemphigus vulgaris*, the blister occurs just above the basal layer, and in *Pemphigus foliaceus* it occurs in the granular layer [2]. The pathologic mechanism of *Pemphigus* is unclear, especially how the bone marrow cells generate autoantibodies to the desmosomes. However, in the early 1990's, the exact targets of *Pemphigus* sera were confirmed as desmogleins, which are the major cadherin-type transmembrane glycoproteins in the desmosomes [3]. The desmoglein-1 isoform is the target of *Pemphigus foliaceus*, and desmoglein-3 is that of *Pemphigus vulgaris* [4,5]. Furthermore, some *Pemphigus vulgaris* patients have not only anti-desmoglein-3 antibodies, but also anti-desmoglein-1 antibodies [6]. *Pemphigus vulgaris* patients with only anti-desmoglein-3 antibodies have predominantly the mucous membranes affected, while those with both anti-desmoglein-3 and anti-desmoglein 1 antibodies tend to have both the mucous membranes and skin affected [6].

As mentioned above, IgG-type autoantibodies against the cell surface of keratinocytes are found in *Pemphigus* patients [7]. Basically, a direct immunofluorescence test for human

IgG on the cell-cell junctions in the epidermis of the perilesional skin is the major diagnostic hallmark of *Pemphigus* [8]. Moreover, the patient's sera are also positive in the indirect immunofluorescence test [7]. In addition, antigen-specific enzyme-linked immunosorbent assays (ELISA) have recently been developed [9].

As *Pemphigus* is an autoimmune disease, many difficulties exist in diagnosing, prospecting prophylaxis, and treating patients correctly. Especially, how *Pemphigus* patients can be treated with minimal side effects, how to induce the drug-free stage, and how to prevent *Pemphigus* in people with a genetic predisposition to the disease. Moreover, current conventional methods in these areas to overcome this devastating disease are still lacking. Over the past 20 years, many patents associated with research, prophylaxis, and the diagnosis and treatment aspects of *Pemphigus* have been reported. In order to obtain an overview of new advances in the field, U.S. patents disclosed from 1988 to 2006 were screened using the internet program DELPHION with input terms "pemphigus," "autoimmune bullous disease," and "desmosome." Through this approach, we found 124 U.S. patent collections. As a result, 124 patents corrected seem to be directly related to pemphigus. These are categorized as 1) diagnosis or prophylaxis 2) animal models, and 3) treatments of pemphigus.

PATENTS RELATED TO THE DIAGNOSIS OR PROPHYLAXIS OF PEMPHIGUS

As mentioned above, the diagnosis of *Pemphigus* is currently dependent on immunological approaches. Moreover, it takes several days to obtain the correct diagnosis. In addition, there have been few ways to predict which people are more likely to develop pemphigus. As a result, there have been numerous patents related to diagnosis over the past 20 years. As to the genetic relationship, *Pemphigus vulgaris* patients tend to have a certain type of class II major histocompatibility complex (MHC) antigens. Among them, the HLA-DR4 or DQ1 haplotype is predominant in certain ethnic groups [10]. In patients with the DR4 serotype, almost

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all have an allele called DR 1*0402, while patients with the DQ1 serotype almost all have an allele called DQ 1*0503 [2]. In order to identify these pemphigus-related HLA types in *Pemphigus* patients, several patents have been proposed. U.S. Patents No. 6194561 and 5665548 disclose the characterization and detection of sequences associated with *Pemphigus* [11,12]. In these patents, Erlich and Horn proposed that the codon encoding the amino acid at position 57 of the HLA-DQ protein sequences and corresponding DNA sequences are associated with pemphigus. They also suggest that the sequences may be used to generate DNA hybridization probes or antibodies for assays to detect a person's susceptibility to both diseases. Several patents, including U.S. Patents No. 5663047, 5976789, 5567809, and 5552275 disclosed and described methods, probes, systems or reagents for HLA DR or its related types in *Pemphigus* [13-16]. U.S. Patent No. 5541065 discloses a method for HLA DP typing [17]. Moreover, several patents potentially impact detecting polymorphisms or HLA related genes or proteins so that clinicians may use them to diagnose *Pemphigus* or to predict those with a genetic predisposition for *Pemphigus* [18-64]. These patents are summarized in Table 1. As a whole, there have been numerous methodologies proposed to detect possible pemphigus-related genes (30 patents) and proteins/peptides (12 patents). Current advancements in array technology may lead to rapid and correct diagnoses or the prognosis of *Pemphigus* in the near future.

Table 1. Patents Related to the Diagnosis of *Pemphigus* by Detecting Specific Gene or Peptide Sequences

1) Method for targeting <i>Pemphigus</i> related genes
-array-based approach [18-39]
-non-array-based approach [11-17, 40-50]
2) Method for targeting <i>Pemphigus</i> related proteins
-array-based approach [51,52]
-non-array-based approach [11-17,46,47,53-60]
3) Others
determining receptor-ligand binding of <i>Pemphigus</i> [61,62]
method for information storage and recovery [63]
method for detecting pemphigus-related signal molecules [64]

ANIMAL MODELS OF PEMPHIGUS

Patents directly related to *Pemphigus* research are related to animal models. Several *Pemphigus* mouse models have been reported. Firstly, the passive transfer model of pemphigus sera or affinity-purified IgG to neonatal mice cause the development of blisters and erosions that clinically and histologically mimic *Pemphigus* [65,66]. In addition, as discussed later, Amagai *et al.* established excellent active animal models of *Pemphigus vulgaris* [67,68]. In U.S. Patent No. 7060868, recombinant desmoglein-3 was injected into "desmoglein-3 genetically deleted mice (desmoglein-3 knock out mice)" so as to generate an immune response against desmoglein-3. After the passive transfer of splenic lymphocytes from these immunized mice to RAG2-/- immunodeficient mice, the latter developed lesions that are

typical of *Pemphigus vulgaris* clinically (blisters in the oral mucosa and disappearance of hair) and pathologically and surprisingly have anti-desmoglein 3 antibodies. Furthermore, these mice have almost identical histopathologic characteristics of pemphigus. They also suggest that these systems may be propagated to construct various autoimmune disease models. Owing to this significant advancement, future development of new therapeutics or new methodologies for diagnosing *Pemphigus* patients may progress rapidly.

TREATMENT OF PEMPHIGUS

As *Pemphigus* belongs to the autoimmune diseases, the treatment of *Pemphigus* should focus on suppressing the immune system. As such, systemic intraoral glucocorticoid therapy combined with immunosuppressive agents, such as mycophenolate mofetil, azathioprine, and cyclophosphamide is used as the conventional therapy for *Pemphigus* [2, 69, 70]. These therapies dramatically improve the mortality and morbidity of pemphigus, although special attention should be paid to the side effects of the therapy, because these treatments target the "entire" immune system; for example, infection, diabetes, pancytopenia, gastrointestinal ulcer, liver/renal function abnormalities, hypertension, electrolyte disturbances, osteoporosis, and so on. If standard therapy is ineffective, additional therapy is sometimes required; for example, the intravenous pulse therapy using methylprednisolone [71], intravenous pulse therapy with cyclophosphamide combined with or without methylprednisolone [72], plasmapheresis [73], or intravenous use of gamma globulin [74]. Although less common, cyclosporine, gold, antimalarials, or dapsone are also sometimes used; and extracorporeal photochemotherapy have been rarely selected [75]. However, immunosuppressant therapies also have severe side effects, a high mortality, and many patients resist therapies. Many of the adverse events occur because these therapies are directed towards the "entire" immune system. Thus, disease specific treatment is needed. Numerous patents related to the treatment of *Pemphigus* have been disclosed. Among them, patents which are designed specifically towards *Pemphigus* therapeutics are discussed first; then we briefly summarize therapies that potentially affect *Pemphigus* (Table 2). Therapies specifically targeted towards *Pemphigus* are categorized into 6 areas; 1) immunosuppressive/non-suppressive chemical compounds, 2) inhibitors which target MHC class II, 3) protease-based therapy, 4) macrolides, 5) nicotinamides, and 6) immunoglobulin therapy.

1. Immunosuppressive/Non-Suppressive Chemical Compounds

U.S. Patents No. 7084247 (Rasmussen and Yu) and 5874531 (Strominger and Wucherpfennig) disclosed and discovered isolated peptides related to *Pemphigus vulgaris* [76,77]. The peptides are self epitopes from pathogens of *Pemphigus vulgaris*. They proposed that pharmaceutical preparations of this may lead to tolerize or immunize individuals who are suffering from *Pemphigus vulgaris*. U.S. Patents No. 6372800, 6187821, and 5948820 disclose the pharmaceutical use of benzene compounds [78-80]. In these patents, Fujita *et al.* describe that the compound has an excellent immunosuppressive effect and is useful to treat

Table 2. Recent Patents Associated with Pemphigus Treatment

Chemical compounds [76-81, 95-108]
Proteases [82-87]
Nucleotide analogs [109-112]
Nucleotide synthesis inhibitor [113]
DNA vaccination or gene therapy [114-119]
Cytokine inhibitors [120]
Anti-tumor reagents [121,122]
Agonist antibodies [123,124]
Antagonist antibodies [125-130]
Affinity binding of antigenic peptides for MHC [131]
Immune modulators [132-137]
Macrolides [88-91]
New method for administration of cyclosporine [138]
Nicotinamide [92]
Immunoglobulin therapy [94]
Extracorporeal plasmapheresis [139]
Photopheresis [140-144]
X-irradiation [145]

pemphigus. U.S. Patent No. 5514714 discloses methods and polycyclic aromatic compounds containing compositions for treating T-cell-mediated diseases [81]. In this patent, Mecuelo and Lavie propose that hypericin or pseudohypericin and their related compounds, including isomers, analogs, derivatives, salts or ion pairs of hypericin or pseudohypericin, are possibly useful to treat several diseases including *Pemphigus vulgaris*. They also mention that the combination of these compounds and other immunosuppressants are possible alternative therapies for these diseases.

2. Inhibitors which Target MHC Class II

Inhibitors which target MHC class II include U.S. Patents No. 5840835, 5817757, and 5719296 which disclose inhibitors of peptide binding to MHC class II proteins [82-84]. In these patents, Adams *et al.* proposed that the compounds they found are useful to treat and prevent autoimmune diseases including pemphigus.

3. Protease-Based Therapy

U.S. Patents No. 5981256 and 5834290 disclosed recombinant stratum corneum chymotryptic enzyme [85,86]. In these patents, Egelrud and Hansson describe a polypeptide having the amino acid sequence SEQ ID NO:2, or an analogue or variant has stratum corneum chymotryptic enzyme activity and is possibly useful as a treatment or prophylactic agent of pemphigus. U.S. Patent No. 5637616 discloses methods for treating diseases mediated by proteases [87]. In this patent, Duvic and Schroeder describe a unique human epidermal surface antigen, ESA that has diagnostic and therapeutic value for autoimmune diseases including pemphigus.

4. Macrolides

U.S. Patent No. 5286730 discloses a method of treating *Pemphigus* with macrolides [88]. In this patent, Caufield *et*

al. describe a new method comprised of administering an anti-inflammatory amount of rapamycin, alone or in combination with cyclosporine A, orally, parenterally, intranasally, intrabronchially, topically, transdermally, or rectally. They mention that this new method is useful in treating several skin diseases including pemphigus. Below, three patents are related to macrolide derivatives to treat pemphigus. U.S. Patent No. 5349061 disclosed the usefulness of O-heteroaryl, O-alkylheteroaryl, O-alkenylheteroaryl, and O-alkynylheteroarylmacrolides [89]. In this patent, Sinclair *et al.* describe macrolides which they identified as useful in treating several diseases including autoimmune diseases such as pemphigus. U.S. Patent No. 5143918 disclosed halomacrolides and their derivatives as having immunosuppressive activity [90]. In this patent, Bochis and Wyvrat described the usefulness of macrolide immunosuppressants in treating autoimmune diseases including pemphigus. U.S. Patent No. 5064835 disclosed hydroxymacrolide derivatives having immunosuppressive activity [91]. In this patent, Bochis *et al.* describe the usefulness of topical treatments with hydroxymacrolide on pemphigus.

5. Nicotinamides

U.S. Patent No. 6949573 (Bailey *et al.*) discloses that nicotinamide derivatives are useful as PDE4 inhibitors [92]. In fact, some reports associated with nicotinamide as a treatment of *Pemphigus* were reported [93]. In addition to this idea, they describe that nicotinamide derivatives that they invented may be useful to treat numerous diseases including pemphigus.

6. Immunoglobulin Therapy

U.S. Patent No. 6932969 discloses immunoglobulin fractions as having immunomodulatory activity [94]. In this patent, Bourel *et al.* describe a method for preparing immunoglobulin fractions from human polyvalent intravenous immunoglobulins which have an immunomodulatory effect on autoimmune diseases including pemphigus.

In addition, patents not originally designed specifically towards pemphigus, but that mention *Pemphigus* and may possibly be related to *Pemphigus* treatment in the future are summarized in Table 2 [95-145].

CURRENT & FUTURE DEVELOPMENTS

As described above, *Pemphigus vulgaris* can currently be controlled by a variety of treatments. However, the mechanism of the failure to immune system, and the cause of the unusually high level of autoantibody production in the bone marrow is still not understood. Why the exact antibody titer does not always correspond with the state of the disease and why some patients show spontaneous regression is not known. To resolve these issues, new technologies to detect and solve these problems are needed.

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