# Meeting Report of the Pathogenesis of Pemphigus and Pemphigoid Meeting in Munich, September 2016

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Autoimmune blistering diseases are a heterogeneous group of about a dozen complex disorders that are characterized by intraepidermal (pemphigus) and subepidermal blistering (pemphigoid diseases and dermatitis herpetiformis). The Pathogenesis of Pemphigus and Pemphigoid Meeting, organized by the Departments of Dermatology in Lübeck and Marburg and the Institute of Anatomy and Cell Biology, Munich, was held in September 2016 in Munich. The meeting brought together basic scientists and clinicians from all continents dedicating their work to autoimmune blistering diseases. Considerable advances have been made in describing incidences and prevalences of these diseases and linking comorbidities with autoantibody reactivities and clinical variants, for example, dipeptidyl peptidase-IV inhibitor-associated noninflammatory bullous pemphigoid. Although new entities are still being described, diagnosis of most autoimmune blistering diseases can now be achieved using standardized and widely available serological test systems. Various experimental mouse models of pemphigus and pemphigoid disease are increasingly being used to understand mechanisms of central and peripheral tolerance and to evaluate more specific treatment approaches for these disorders, such as molecules that target autoreactive T and B cells and anti-inflammatory mediators, that is, dimethyl fumarate, phosphodiesterase 4, and leukotriene B4 inhibitors in pemphigoid disorders, and chimeric antigen receptor T cells in pemphigus. Very recent experimental data about the immunopathology and the determinants of autoantibody formation and keratinocyte susceptibility in pemphigus were discussed. With regard to cellular mechanisms leading to the loss of cell-cell adhesion, new ideas were shared in the field of signal transduction. Major steps were taken to put the various partly contradictory and controversial findings about the effects of pemphigus autoantibodies and other inflammatory mediators into perspective and broaden our view of the complex pathophysiology of this disease. Finally, two investigator-initiated multicenter trials highlighted doxycycline and dapsone as valuable medications in the treatment of bullous pemphigoid.

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*Abbreviations: AIBD, autoimmune blistering disease; BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; MMP, mucous membrane pemphigoid; PV, pemphigus vulgaris*

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## INTRODUCTION

After successful international meetings on autoimmune blistering diseases in Salzburg (1998), Otsu (2008), and Lübeck (2013), we met in Munich September 5−7, 2016 to discuss recent advances in the understanding of these complex prototypic autoantibody-mediated disorders (Figure 1). Plenary lectures were given by the authors flanked by oral presentations selected from the 66 abstracts that were discussed in a poster session. The first day was dedicated to all aspects of the different pemphigoid diseases, and the second day focused on the pathogenesis of pemphigus disorders.

## PEMPHIGOID DISORDERS

### Epidemiology

Although the incidences of autoimmune blistering disease (AIBD) have been studied in a variety of different populations, data about the prevalence of these disorders are sparse. Franziska Hübner of Lübeck, Germany, collaborated with the largest German health insurance company, the Techniker Krankenkasse. Based on coding from the *International Classification of Disease, 10th revision* (World Health Organization, 1990) she calculated a total number of 40,400 patients (0.05% of a population of 80,925,000) with autoimmune blistering diseases in Germany in 2014 (Hubner et al., 2016). Bullous pemphigoid (BP), pemphigus vulgaris (PV), and mucous membrane pemphigoid (MMP) were identified as the most prevalent disorders with adjusted prevalences of 259.3, 94.8, and 24.56 per million inhabitants, respectively (Hubner et al., 2016).

By far the most frequent AIBD, BP is known to be highly associated with old age, distinct drugs, and several neurologic and psychiatric diseases, collectively affecting 30−50% of BP patients. This last observation is particularly intriguing, because BP180 (type XVII collagen), the main target antigen in BP, is expressed in different parts of the central nervous system such as the hippocampus, thalamus, midbrain, and basal forebrain. In line with this, Laura Huilaja of Oulu, Finland, reported that serum levels of anti-BP180 antibodies correlate with more severe dementia and Alzheimer disease, indicating a potential relation between the autoimmune skin disease and the central nervous pathology (Kokkonen et al., 2017). Drug intake as another potential trigger of BP was addressed by Wataru Nishie. Based on the increasing number of dipeptidyl peptidase-IV inhibitor (gliptin inhibitor for diabetic control)−associated BP, his group observed, using a full-length BP180 ELISA, that dipeptidyl peptidase-IV inhibitor−associated BP tends to show a non-inflammatory phenotype and that autoantibodies are more likely to target epitopes on the BP180 ectodomain outside NC16A (Izumi et al., 2016). These data further support previous observations that not all BP patients generate antibodies against the immunodominant NC16A domain of BP180 and that several clinical BP variants exist in addition to the two classical phenotypes, that is, tense blisters and erosions or urticarial plaques and erythema.

Skin microbiota have recently been highlighted as related to disease expression in a variety of inflammatory disorders. Meriem Belheouane presented unpublished work on the role of skin microbiota in modulating BP susceptibility. Using both a human cohort and experimental BP in adult mice, she found that the composition of skin microbiota is associated with disease severity, which supports a role of the skin microbiota in the onset and development of BP.

### Diagnosis

Diagnosis of AIBDs is based on three columns: clinical presentation, direct immunofluorescence microscopy, and detection of serum autoantibodies. Although direct immunofluorescence microscopy can still be regarded as the diagnostic criterion standard, in many patients diagnosis can be made by serological analyses and the clinical picture alone. In pemphigoid diseases, immunoglobulin deposition at the dermal-epidermal junction is not entirely linear but slightly undulated. Two patterns can be observed by direct immunofluorescence microscopy: the u-serrated pattern, with arches closed at the bottom unique to autoimmunity against type VII collagen (epidermolysis bullosa acquisita [EBA] and bullous systemic lupus erythematosus), and the n-serrated pattern, with arches closed at the top. The n-serrated pattern is seen in all other pemphigoid disorders. Pattern analysis is particularly valuable in EBA patients because in this group, serum autoantibodies can be detected in only about half of patients. Although the concept of a pattern diagnostic was developed about a decade ago, it still needs to spread widely in the routine diagnostic workup of AIBDs.

Serological diagnosis of AIBDs has been a rapidly expanding field over the last years. Gabi Ommen of Lübeck, Germany, introduced a previously undescribed multivariant ELISA that compiled six recombinant target antigens, that is, desmoglein 1, desmoglein 3, envoplakin, BP180, BP230, and type VII collagen. In two prospective studies, this ELISA allowed the one-step serological diagnosis of 95% of pemphigus and 71% of pemphigoid diseases and will further facilitate the diagnosis of AIBDs (Van Beek et al., 2017). Another diagnostic approach was chosen by Jane Setterfield analyzing saliva in patients with MMP. With a BP180 NC16A ELISA, reactivity was seen in 45% of MMP patients' saliva compared with 52% in serum. In 64 MMP patients, additional use of saliva increased detection of IgG and/or IgA to BP180 NC16A to 67%, representing a 30% increase (Ali et al., 2016).

### Treatment

On behalf of the UK Dermatology Clinical Trials Network in collaboration with seven German centers, Karen Harman presented the results of the BLISTER trial. This prospective controlled multicenter trial showed that initiation of treatment with doxycycline at 200 mg/day was noninferior in terms of blister control at 6 weeks and superior in terms of number of severe treatment-related events by 52 weeks compared with tapering doses of prednisolone at 0.5 mg/kg body weight/day. This pragmatic trial suggests that for BP patients in whom topical treatment is not possible, a policy of starting treatment with oral doxycycline produces acceptable blister control in the short term and better long-term safety than conventional treatment with oral prednisolone (Williams et al., 2017). Another investigator-initiated multicenter prospective controlled trial in BP investigated the efficacy and safety of