# Research Techniques Made Simple: Mouse Models of Autoimmune Blistering Diseases

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Autoimmune blistering diseases are examples of autoantibody-mediated, organ-specific autoimmune disorders. Based on a genetic susceptibility, such as a strong HLA-class II association, as yet unknown triggering factors induce the formation of circulating and tissue-bound autoantibodies that are mainly directed against adhesion structures of the skin and mucous membranes. Compared with other autoimmune diseases, especially systemic disorders, the pathogenicity of autoimmune blistering diseases is relatively well described. Several animal models of autoimmune blistering diseases have been established that helped to uncover the immunological and molecular mechanisms underlying the blistering phenotypes. Each in vivo model focuses on specific aspects of the autoimmune cascade, from loss of immunological tolerance on the level of T and B cells to the pathogenic effects of autoantibodies upon binding to their target autoantigen. We discuss current mouse models of autoimmune blistering diseases, including models of pemphigus vulgaris, bullous pemphigoid, epidermolysis bullosa acquisita, and dermatitis herpetiformis.

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**Description:** This article, designed for dermatologists, residents, fellows, and related healthcare providers, seeks to reduce the growing divide between dermatology clinical practice and the basic science/current research methodologies on which many diagnostic and therapeutic advances are built.

**Objectives:** At the conclusion of this activity, learners should be better able to:

- Recognize the newest techniques in biomedical research.
- Describe how these techniques can be utilized and their limitations.
- Describe the potential impact of these techniques.

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## INTRODUCTION

Autoimmune blistering diseases (AIBDs) are a group of rare acquired blistering skin diseases that are divided into four major groups based on clinical appearance and pathology: pemphigus diseases, including the most common clinical subtypes pemphigus vulgaris (PV) and pemphigus foliaceus, the pemphigoid diseases like bullous pemphigoid (BP), epidermolysis bullosa acquisita (EBA), and dermatitis herpetiformis (DH). These diseases share the common feature of being caused by circulating autoantibodies targeting

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*Abbreviations: AIDB, autoimmune blistering disease; BP, bullous pemphigoid; COL-17, type XVII collagen; COL-7, type VII collagen; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; MHC, major histocompatibility complex; PV, pemphigus vulgaris*

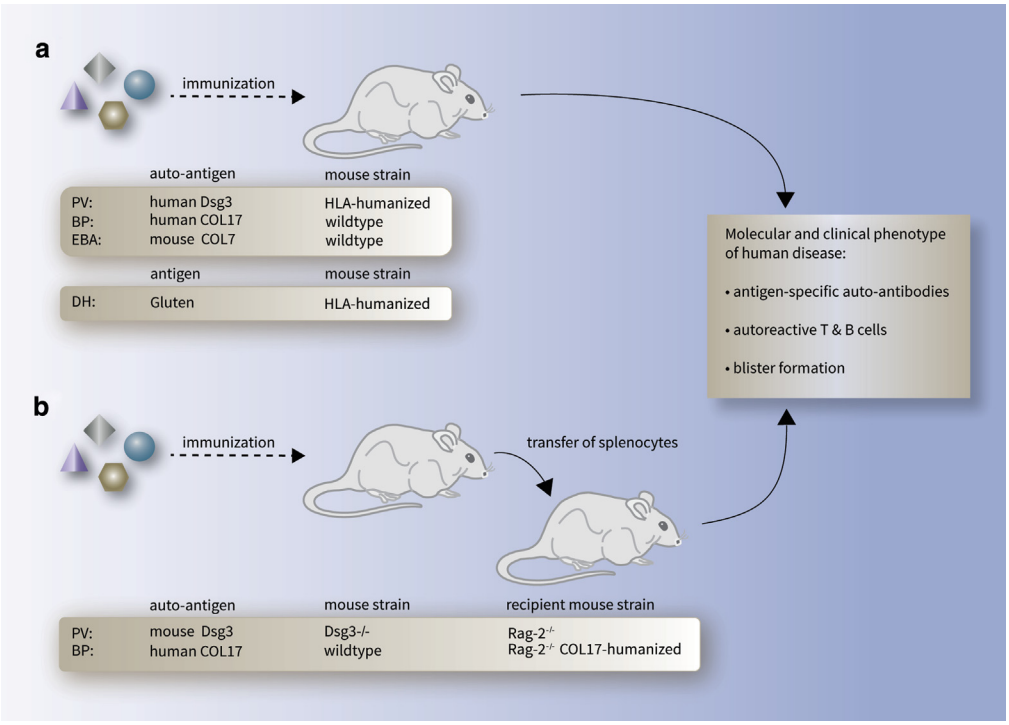


**Figure 1. Mouse models of autoimmune blistering diseases.** Autoantigens and mouse strains used for immunization are shown for each respective autoimmune blistering disease. (**a**) Current animal models for PV, BP, EBA, and DH use wild-type or humanized HLA-transgenic mice. Some models are limited because of weak homology between human and mouse proteins and established self-tolerance to autoantigens in mice. (**b**) To avoid the difficulty of self-tolerance, preventing the mouse immune system from reacting destructively against autoantigens of the skin, enhanced models for PV and BP use immunization of mice lacking the autoantigen. After subsequent adoptive transfer of splenocytes (containing autoreactive T and B cells) in *Rag2*-knockout recipient animals expressing the autoantigen, an autoimmune response is initiated that resembles certain aspects of the human disease. BP, bullous pemphigoid; COL7, type VII collagen; COL17, type XVII collagen; DH, dermatitis herpetiformis; Dsg3, desmoglein 3; EBA, epidermolysis bullosa acquisita; PV, pemphigus vulgaris.

**Table 1. Models of AIBD using active immunization with the respective antigens**

| Blistering Disease | Purpose of Model | Methods Used in the Model | References |
|---|---|---|---|
| PV | Generation of mouse Dsg3-specific T and B cells and characterization of produced autoantibodies; induction of a clinical phenotype in mouse | Immunization of Dsg3 knockout mice with mouse Dsg3 and subsequent transfer of splenocytes into Dsg3-competent immunodeficient *Rag2*-knockout recipients | Amagai et al., 2000; Tsunoda et al., 2003; Takahashi et al., 2008 |
| | | Transfer of Dsg3 knockout splenocytes into immunodeficient *Rag2*-knockout, Dsg3-competent recipients | Aoki-Ota et al., 2004; Kawasaki et al., 2006 |
| | Study the role of HLA molecules in loss of self-tolerance against human Dsg3 | Immunization of humanized HLA-transgenic, MHC class II knock-out DBA/1J mice with human Dsg3 | Eming et al., 2014; Schmidt et al., 2016 |
| BP | Characterize human COL17-specific T and B cells in initiation and effector phases of disease | Human COL17 immunization of wild-type mice by skin grafting from humanized COL17-transgenic mice | Olasz et al., 2007 |
| | | Human COL17 immunization of wild-type mice by skin grafting from humanized COL17-transgenic mice and subsequent transfer of splenocytes in COL17-humanized *Rag2*-knockout mice | Ujiie et al., 2010 |
| EBA | Characterize loss of self-tolerance against COL7 and the mechanisms of autoantibody-induced tissue damage | Immunization of SJL/J mice with mouse GST-tagged COL7C | Ludwig et al., 2011; Sitaru et al., 2006 |
| DH | Study the role of HLA molecules in disease induction after gluten-sensitization | Gluten-sensitization of HLA-DQ8 −transgenic, MHC class II knockout NOD mice | Marietta et al., 2004 |

Abbreviations: BP, bullous pemphigoid; COL, collagen; DH, dermatitis herpetiformis; Dsg, desmoglein; EBA, epidermolysis bullosa acquisita; GST, glutathione S-transferase; MHC, major histocompatibility complex; NOD, nonobese diabetic; PV, pemphigus vulgaris.

disease-specific autoantigens in the human skin, resulting in painful blisters of the skin and/or mucous membranes. Several mouse models of AIBD have been generated, allowing researchers to investigate key pathophysiological mechanisms. These models are either *passive*, based on the transfer of previously generated autoantibodies into mice to generate a blistering phenotype in vivo, or *active*, based on immunization of wild-type or genetically modified mice with the