031 Development of a mouse model of Pemphigus Vulgaris as a tool to evaluate nanoscale peptide-bound antibody-induced T cell tolerance

C. Hutzler1, M. Hering1, R. Eming1 and R. Stary1,2,6
1 Department of Dermatology and Allergology, Philippus-University Marburg, Marburg, Germany and 2 Topas Therapeutics GmbH, Hamburg, Germany

Pemphigus Vulgaris (PV) is an autoimmune blistering disease caused by autoantibodies mainly directed against desmoglein (Dsg). So far, only broad systemic immunosuppression and B-cell depletion are being applied in PV patients. In this study, we aim at investigating a Dsg3-specific CD4+ T cell directed therapy in PV. We apply human leukocyte antigen (HLA)-transgenic mice expressing the PV-associated HLA-DRB1*04:02 for peptide-induced T cell tolerance. PV mice were immunized with a peptide corresponding to the human CD4 coreceptor and lack mouse MHC class II (I-A/I-3). Immunization with recombinant human Dsg3 protein leads to induction of Dsg3-specific CD4+ T and Dsg3-reactive IgG producing B cells. In addition, 7% of the CD11c+ DCs were colocalized with CD4+ T cells around hair follicles. Additionally, these CD11c+ DCs were also observed in the dermis at day 35 after the resolution of ear swelling and expressed CD69, a specific T cell tolerance induction into the clinic. Preclinical proof of concept results hold great promise to translate the concept of Dsg3-directed T-cell immunotherapies to the clinic. These preclinical results hold great promise to translate the concept of Dsg3-specific T cell tolerance induction into the clinic.

032 An advanced biology platform to guide the discovery of a new highly selective JAK1 inhibitor for atopic dermatitis treatment

G. Neumann1,2,6,4, B. Jäger1, C. Leist1,2,6, J. Van den Bogaert1, L. Bittecker1,2 and R. Stary1,2,6
1 Department of Dermatology and Allergology, Philippus-University Marburg, Marburg, Germany, 2 Topas Therapeutics GmbH, Hamburg, Germany and 4 Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

Expansion of BCL2+ lymphocytes in cutaneous graft-versus host disease is associated with steroid resistance and poor prognosis

J. Strobl1, R. Pandey1, T. Kaugrauber1, F. Tinnefeld1, L. Kleissl1, M. Hara1, W. Rabitsch2, C. Bock2, G. Hopfer2 and R. Stary1,2,6
1 Department of Dermatology, Medical University of Vienna, Vienna, Austria, 2 German Research Center for Molecular Medicin of the Austrian Academy of Sciences, Vienna, Austria, 3 Clinical Institute for Pathology, Medical University of Vienna, Vienna, Austria, 4 Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria, 5 Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria and 6 Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria

Bacterial infection of host skin tissue (GVHD) may induce a major role of atopy and alloimmune hematopoietic stem cell transplantation (HSCT) in response to first-line therapy with glucocorticoids is often limited. To identify novel therapeutic targets for treatment and prophylaxis of GVHD, we developed the murine leukocyte antigen (HLA)-encoded transmembrane protein (TMEM173) in vitro and in vivo. Elevated TMEM173 expression levels are associated with steroid-refractory GVHD and increased transplant-related mortality. These results indicate that CD4+ TRM cells retain after clinical resolution of skin inflammation and are required to navigate transiently in spleen shortly after Dsg3-immunization (day 6) and cannot be detected at day 21 anymore. However, at day 21 Dsg3-specific plasma cells can be identified in bone marrow shown by Dsg3-specific B-cell ELISPOT analysis. For induction of Dsg3-specific T cell tolerance, we applied a set of immunodominant Dsg3 CD4+ T cell epitopes linked to nanoparticles in a preclinical mouse model of PV. These preclinical results hold great promise to translate the concept of Dsg3-specific T cell tolerance induction into the clinic.

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1 Department of Dermatology, Medical University of Vienna, Vienna, Austria, 2 German Research Center for Molecular Medicin of the Austrian Academy of Sciences, Vienna, Austria, 3 Clinical Institute for Pathology, Medical University of Vienna, Vienna, Austria, 4 Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria, 5 Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria and 6 Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria

Characterization of novel TMEM173 mutation causing a lupus- and SAVI-like phenotype, modified by polymorphisms in TMEM173 and IFRH1

S. Keskkala1, E. Haapamäki1, E. Einarisott1, K. Rajamäki1, J. Saarela1, J. Jere1, M. Seppänen1, J. Ranki2, S. Eirefelt1, H. Siller1 and J. Correa da Rosa1
1 LEO Pharma A/S, Ballerup, Denmark and 2 Institute of Dermatology, University of Helsinki, Helsinki, Finland

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035 Targeted inhibition of complement at the basement-membrane zone in pemphigoid diseases

C. Hammer1, S. Entemanni1, O. Iksen1, N. Tautz1, E. Schmied1, D. Siegel1 and R. Stanley1
1 Dermatology, University of Pennsylvania, Philadelphia, PA, 2 LHD, University of Luebeck, Luebeck, Germany, 3 Pathology and Laboratory Medicine, University of Pennsylvania, Pennsylvania, PA and 4 Virology, University of Luebeck, Luebeck, Germany

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Bullous pemphigoid (BP) and mucous membrane pemphigoid (MMP) are blistering skin diseases in which autoantibodies against basal keratinocyte antigens cause loss of cell-cell adhesion in the basement membrane zone (BMZ). Biologics usually show BMZ-binding IgG and C3 in direct immunofluorescence (IF), indicating complement activation that results in attraction and activation of inflammatory cells and subsequently dermal-epidermal separation. We cloned more than 30 anti-BP180/BP230 single chain variable fragment (scFv) from a library of transgenic mice specific for BP180 and tested 12 representative BP patients. All mAbs were validated by in vitro ELISA and indirect IF. Unexpectedly, our scFvs displaced bound patient IgG from the immobilized antigens in vitro. Confirming previous data, monovalent anti-BP180 scFv fusion protein (gigastasin) and anti-BP230 scFv inhibited IgG binding to human skin organ culture, indicating that the monoclonal antibody binding to the chronic phases of the disease. Accordingly, clinical efficacy has been shown for biologics targeting JAK1-related cytokines, e.g., IL-11, IL-12 and IL-31 and for small-molecule JAK inhibitors. In particular, the second-generation selective JAK1 inhibitors are proposed to provide a more favorable risk-benefit treatment profile, given their greater selectivity. Here we describe a JAK1 in vitro biological platform based on several biochemical and biological assays rationally designed to consistently address selectivity and potency. Through this platform, we discovered a potent and selective JAK1 inhibitor, LEO42397, with cellular and whole blood activity that parallels its potency and selectivity throughout all the assays. Further, LEO42397 showed in vivo efficacy in a mechanistic mouse model addressing target activity in the skin as well as an attractive oral drug-like properties and safety profile, supporting its clinical development as treatment of atopic dermatitis. Finally, we used our JAK1 in vitro biological platform to compare the potency and selectivity of a panel of JAK inhibitors that are either launched or in clinical development. In our assays only LEO41397, abrocitinib and to some extend itacitinib were found to be highly selective JAK1 inhibitors. Our work highlights the importance of using a translational in vitro platform when addressing and interpreting JAK1 selectivity.