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Title: Deficient autophagy in Hermansky-Pudlak syndrome associated interstitial pneumonia (HPSIP)

Mr. Saket 29796 Ahuja saket.biotech@gmail.com [1], Dr. Ingrid 29797 Henneke Ingrid.Henneke@innere.med.uni-giessen.de [1], Dr. Lars 29798 Knudsen Knudsen.Lars@mh-hannover.de MD [2], Dr. Bernadette R. 29799 Gochuico gochuicb@mail.nih.gov [3], Dr. Clemens 29800 Ruppert Clemens.Ruppert@innere.med.uni-giessen.de [1], Prof. Dr Matthias 29808 Ochs ochs.matthias@mh-hannover.de MD [2,4], Dr. Martina 29810 Korfei Martina.Korfei@innere.med.uni-giessen.de [1], Prof. Dr Werner 29812 Seeger werner.seeger@innere.med.uni-giessen.de MD [1,5], Prof. Dr Andreas 29828 Guenther andreas.guenther@innere.med.uni-giessen.de MD [1,5,6] and Dr. Poornima 29896 Mahavadi Poornima.Mahavadi@innere.med.uni-giessen.de [1]. [1] Department of Internal Medicine, University of Giessen and Marburg Lung Center, Giessen, Germany, 35392 ; [2] Institute for Functional and applied anatomy, Hannover Medical School, Hannover, Germany ; [3] Medical Genetics Branch, National Human Genome Research Institute (NHGRI), Bethesda, United States ; [4] German Center for Lung Research, (DZL), Hannover, Germany ; [5] German Center for Lung Research, (DZL), Giessen, Germany and [6] Agaplesion Lung Clinic, Waldhof Elgershausen, Greifenstein, Germany .

Body: Introduction: Hermansky-Pudlak syndrome (HPS) is a lysosome realated disorder. Patients with HPS types -1, 2 & 4 develop pulmonary fibrosis called Hermansky-Pudlak syndrome associated Interstitial Pneumonia (HPSIP). HPSIP lungs show enlarged alveolar typeII cells (AECII) with giant lamellar bodies. We previously reported lung fibrosis in a HPSIP mouse model (HPS1/2), accompanied with surfactant accumulation and apoptosis of AECII due to severe lysosomal and ER stress in these mice. Data from human HPS1 patient corroborated with the HPS1/2 mice data. We aim to analyze autophagy, a lysosomal degradation pathway in HPSIP. Methods: Immunohistochemistry was performed on serial paraffin lung sections from HPS1, 2, 1/2 and WT mice, lung sections from human HPS1 patients and healthy donors for autophagy related proteins LC3, p62 and for AECII marker, pro SP-C. Immunogoldlabelling for LC3B was performed on mice lungs fixed in paraformaldehyde and gluteraldehyde. Results: Immunohistochemistry revealed that the AECII of HPS1/2 mice and human HPS1 did not stain for LC3B, while a convincing signal was observed within macrophages of the same sections and within AECII & macrophages of WT mice and healthy donors. Electron microscopy results confirm the qualitative observation of less labeling of LC3B on the limiting membrane of lamellar bodies in HPS mice compared to WT mice. Immunohistochemistry showed decreased staining for p62 within AECII of HPS1/2 compared to WT mice. Conclusion: Our results point towards defective autophagy under HPSIP conditions both in mice and men. An indepth analysis of this pathway is underway to further understand the role of defective autophagy in the development of

HPSIP.