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**Title:** Pulmonary alveolar proteinosis: iPS derived macrophages as in-vitro disease model and potential source for novel gene and cell therapies

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**Body:** Hereditary Pulmonary alveolar proteinosis (PAP) is caused by mutations in the GM-CSF receptor genes (CSF2RA/B) resulting in an inability of macrophages to clear alveolar spaces from protein. Patients suffer from life-threatening respiratory insufficiency, and treatment options are extremely limited. As induced pluripotent stem cells (iPS) were advocated as valid disease models and source for autologous cell or gene therapy, we generated iPS from a CSF2RA-/- PAP patient. Using lentiviral transduction, CD34+ cells were reprogrammed and three iPS clones with typical gene expression, methylation pattern, differentiation capacity, and absence of chromosomal abnormalities were obtained. Myeloid differentiation of these PAP-iPS clones yielded monocyte/macrophages (MM) of typical morphology and surface phenotype. Basic inflammatory functions were normal, but GM-CSF dependent functions such as CD11b activation, GM-CSF uptake and downstream signalling were significantly reduced as compared to control MM derived from healthy embryonic stem cells. Importantly, lentiviral gene correction led to stable and longterm CSF2RA-expression in PAP-iPS which was maintained during all steps of myeloid differentiation. Functional analyses of such gene corrected MM demonstrated almost complete restoration of GM-CSF dependent functions. Our results introduce myeloid differentiation of patient-specific iPS as a relevant in-vitro model for PAP. Moreover, as intratracheal transplantation of healthy MM has been shown to be effective therapy in murine PAP, we suggest in vitro generated gene-corrected monocytes as a promising source for novel therapies in hereditary PAP.