**Comments to the Editor:**

Kasperman et al describe their attempt at generating a repository of iPSCs collected from two AATD clinical trials. The authors reprogramed iPSC lines from 28 patient samples and characterized 10 of them in this study and differentiate them into hepatocyte like lines and Lung progenitor with NKX2-1 positivity. Authors use RNAseq to evaluate their differentiated cells.

While there is merit in this study, the study lacks a lot of experiments in validating the lung progenitor lines and their capacity to model disease. The goal of this study is to establish differentiate cells to model disease phenotypes, however there is not enough data to support these claims. Additionally, there are more data into the hepatic cells than the lung cells in this study. The authors may benefit from submitting this manuscript into a more appropriate journal. Please see the “main major comments” in the comments to author section for reference.

I chose to reject this manuscript as the experiments needed to bring this manuscript to acceptable quality might require a long time. However, I am happy to re-evaluate the manuscript in case of a major revision.   
I performed this review with help of my supervisor Dr. Darcy E. Wagner.

**Comments to the authors:**

Kasperman et al. describes a repository of alpha-1 antitrypsin deficiency (AATD) patient-specific iPSCs for disease modeling. The authors collected the samples from patients enrolled in two clinical trials. iPSCs were reprogrammed from either peripheral blood mononuclear cells (PBMCs) or dermal fibroblasts. The authers collected 150 samples of different AATD genotypes and selected 10 of the most common types and differentiated them into hepatocytes (iHep) and NKX2-1 expressing lung cells that are (CD47high / CD26low). The authors performed RNAseq on the differentiated and undifferentiated iPSCs to characterize them. CRISPR-Cas9 was also used to correct some of the AATD mutations in the SERPINA1.

1. Main major comments:
   1. The authors mention the difficulties in sharing patient materials between academic institutes. To this end, the authors obtain consent from the patients of which samples were collected. However, it is not clear what these consent forms may allow for. What is different in this study that may allow for sharing of these samples and what are the limitations of this repository? An example, can these cell lines be shared internationally?
   2. The authors use primary adult human hepatocyte cells (PHH) to compare their iHep cells with. However, there are no such experiments done for the lung cells. The authors must validate the lung differentiated iPSCs against primary lung cells.
   3. The authors present their study as a model to study disease phenotype in differentiated cells. However, the authors do not show any functional experiments for the differentiated lung progenitors. The NKX2-1 positivity only shows the
   4. Will the RNAseq data be deposited and made publicly available?
   5. Are lines able to differentiate into lung and liver cells after the mutation correction?
   6. If the intention is to use these iPSC lines as disease models, may the authors show the ability of CRISPR-Cas9 mutation correction after the cells have been differentiated?
2. Specific major comments:
   1. On Page 10, authors mention: “ iHeps differentiated from these 10 featured iPSC lines in these experiments consistently acquired a characteristic hepatocyte-like morphology”. There is no morphology data shown. Authors cite previously published data. It is not clear whether the same lines were used in the previous publication in 2015 or if the purpose of the citation was to refer to the intended morphology. In the case of the latter, the authors must show data to support this statement.
   2. The markers used to validate iPSCs in figure E1 are ambiguous. The authors should indicate which staining were used in their panels.
   3. In figure 2, authors show the ability of differentiated iHep to retain AAT expression. Are the differentiated lung progenitors able to accomplish the same?
   4. In figure 3, did the authors use all the genes on the PCA analysis. If the authors did some pre filtering of the data, it must be reported.
   5. In figure 3, what gene lists where used to obtain enrichment scores on GSVA?
   6. In Figure 3E, what does the percentage NKX2-1 enrichment refer to? Compared to what? And based on what were the cut off values were selected to choose the 30 genes.
   7. In Figure 3E and table E3, how specific are these genes to the hepatic lineage?
   8. The authors chose to perform mutation correction on two lines isolated from the same patient (100-3). However, it is not clear whether the results shown are a combination of both or only one of the them. The authors should clarify the experimental set up.
   9. iPSCs from 100-3 were used for mutation correction study. However, the clinical information for this patient was not included. Authors should reason their choice of line for mutation correction experiments.
   10. The authors must show the capacity of the iPSCs with corrected mutations to differentiate into lung or liver cells.
3. Minor Comments
   1. In the abstract:
      1. Expand on background info.
      2. Clarify that n=150 is number of patients. It should also be indicated that only 28 iPSC lines were reprogrammed in this study.
   2. Table 1 & 2, what is the gender distribution among the 10 selected lines?
   3. Tables 1 and 2, authors must indicate the source of the selected lines (PBMC vs skin).
   4. Abbreviations used without definition in supplements (MR, CJ).