Reviewer's report

Title: Limitations in high-throughput drug screening on a cellular model for Friedreich ataxia

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Reviewer: Francesc Palau

Reviewer's report:

The authors set out a high-throughput drug screening in a cell model of Friedreich ataxia (FRDA), which represents the first reported attempt to search for drugs in a cell-based assay that might be useful in the treatment of the disease. The investigators generate a targeted ribozyme strategy in mouse fibroblasts and they have investigated the effect on cell growth and several iron-sulfur clusters (ISC) proteins activities when screening the 1,120 compounds of the well-established Prestwick Chemical Library. The finally did not obtained any noteworthy result for any molecule. However, both the strategy to generate of the cellular model and the protocol they follow to test the full library are very well designed. While it could be think that the absence of positive results may preclude the interest of such a kind of report, I think it represents a kind of research that is important to be reported and relevant for the researchers in the field. This is especially true when considering the need to have appropriate cell models to investigate drug response and search for new potential drugs in FRDA and other rare genetic disorders with no effective treatment.

Drug screening is performed in the R2C1 immortalized fibroblast line with originally showed significant protein and mRNA reduction to 10% and 16%, respectively, when compared to the heterozygous compound control FrdaL2+/L- (50% of frataxin). This represents a strong reduction of the protein as expected for a good cell model of frataxin deficiency. Interestingly, after numerous passages the mRNA level increases to 29%. In such a case the biochemical pattern of ISC protein activities in normalized indicating an important change in the experimental status. This is an added difficulty in this kind of experimental studies.

I have no any major criticisms to the paper in the whole design, results and discussion but I have just a few minor criticisms and comments:

1. The chosen cell is the murine fibroblasts. This cell is useful and very frequently used by investigators but it is not the candidate cell to be tested in a cellular model. Efforts generating different cell models for FRDA are really needed in order to have good correlation between the bench results (always very difficult) and the results in clinical trials.

2. Page 14, lane 11: when the frataxin expression increase is mentioned it is referred to wild type level. This is not a correct expression as the control level is 50% from the compound heterozygous fibroblasts. It should be change to control cells level or similar.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.