

25th April 2022

Dear Board of Trustees,

On behalf of the Research Review Committee of the CASK Research Foundation, I am pleased to inform you that we unanimously support the application of the UC Davis Team, led by Dr Kyle Fink, for funding of their research project. CASK is classed as a rare genetic disease that causes severe disabilities in paediatrics and currently has no treatment. Primary research into investigating gene therapy is the only viable hope for a long-term treatment for CASK that could significantly improve the lives of CASK patients.

The proposal from this team describes a scheme of work aiming to reactivate the healthy copy of the *CASK* gene in an *in vitro* neural cell model based on induced human pluripotent stem cells, and parallel work in genetically modified mice that express approximately one third the normal level of CASK protein. The project's aims are ambitious, both technically and conceptually, however the researchers involved have suitable experience to overcome any challenges that might reasonably arise, have considered possible alternative routes to success should problems occur, and have a proven track record in many of the required techniques for x-linked gene reactivation through their work on the *CDKL5* gene and its associated disorder, and on the *MECP2* gene linked to Rett syndrome.

If the project proceeds as planned, we believe that the outcomes will offer several benefits to the field that are relevant and align well with the CASK Research Foundation's mission. The data generated will likely be published in a high-impact scientific journal, which will raise awareness of CASK gene mutations as a viable field of research for other groups, as well as providing important validation of the CASK model mouse, which is currently lacking. The work done on the mouse model will be a crucial foundation for any future non-clinical work that would be required to take the project from research bench to the clinic. The project can be expected to ascertain whether CASK reactivation is a feasible therapeutic avenue. If it is, the data generated can then form the basis for further grant applications to larger funding bodies, with the intention to initiate clinical trials once sufficient data are available to support biological proof-of-concept and a suitable toxicity profile.

Outside of the CASK research field, the project offers a platform approach for the treatment of other diseases that would respond to gene reactivation, making it a wide-ranging technology to treat rare genetic diseases. The technology to be used for X-linked gene reactivation in CASK is based on CRISPR gene editing, which is now well-recognised as a promising and viable means for treating patients. Numerous clinical studies using CRISPR have been approved by the regulatory authorities for treatment of both genetic diseases (including sickle cell disease, beta-thalassemia, degenerative retinal disorders) and oncology indications. Studies are ongoing globally (US, Canada, Netherlands, Germany, Italy, Spain, UK, Australia, China) and some include paediatric patients ( $\geq 2$  years old), indicating that regulators consider this technology as suitable for treating even very young patients and benefits outweigh the potential risks. The full list of registered clinical trials using CRISPR technology is attached (source: [clinicaltrials.gov](https://clinicaltrials.gov)).

The project budget appears to be measured and reasonable for the group's aims, although current global instability makes future cost projection a real challenge. We would advise caution in this regard and encourage the Board to consider a ten percent contingency on top of the stated figures. There is the option that if sufficient proof-of-concept data are obtained before project completion, alternative funding applications could be made to take over as primary funding source of the project, but this cannot be relied upon. If the Board has any further questions or would like additional detail on the basis of this recommendation, then we would be happy to discuss it further.

Dr Lucy Robinson – Chair

