CRACK IT

Challenge 12: Untangle

Q. **The Phase 1 deliverables include identifying sources of cells from patients and healthy individuals. What if you already have suitable cells for the project?**

A. That would be a great advantage. You would have to justify whether you needed all the available resources for Phase 1. An application for Phase 1 is still required even if you do not require funding.

Q**. Should the cell system express an adult phenotype re: tau isoforms?**

A. Preferably yes, including adult kinase expression.

Q**. Time is short to source cells and get ethical approvals. What kinds of patient samples should be included? How many human mutations for example?**

A. The objective is to have a cell system that demonstrates the required properties of tau expression, aggregation, spread of tauopathy and functional disruption. As long as it delivers, the genetic basis is not critical unless it is believed that the properties of the system are unique to the individual donor. For mechanistic studies it would be useful to have greater diversity of cell samples - at least patient vs normal.

Q**. Not knowing much about the mechanism of tauopathy, how should the system be driven e.g. by inclusion of amyloid?**

A. Probably not amyloid in the first instance, but the choice of cells/mutations/drivers is up to the applicants.

Q**. Patch clamping is the typical electrophysiology method for iPS cells, but showing network function is less common. Which do you require?**

A. The network aspect is important for showing dysfunction.

Q. **Could the project use human ES cells rather than iPS cells as a source of neurons?**

A. Because of ethical concerns, human ES cells are unlikely to be an option for the sponsors.

Q. **What would be the endpoint of the screen?**

A. The ideal screen would be one which could be scaled to provide high-throughput with a simple e.g. biochemical endpoint, but which could also be used with other endpoints (imaging, electrophysiology) to answer more complex questions or to test mechanisms. Automation is also important.

Q. **Would minibrain systems be suitable?**

A. Cell based systems are preferable for simplicity of use and throughput.

Q**. If the preferred theory of tauopathy spread is via the synapse, how important is it to show that in the *in vitro* system?**

A. That would have greater face validity but it may not be critical.

Q. **Would the sponsors provide human material?**

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A. No. The sponsors will provide reagents and undertake validation.

Q**. Why not use primary neuronal cultures from post-mortem human brain?**

A. There are doubts about the continuity of supply and reproducibility of such material. Even so, it could be useful for validation purposes.

Q. **Would a device of the "lung on a chip" type be useful?**

A. Could be great for measuring network function and dysfunction but its scalability might be problematical for screening. Potentially, such a system could be used as a second level screen.

Q. **Would 3D cultures in scaffolds be suitable?**

A. They could be if they solve issues with regular 2D culture. They would need to be transparent, suitable for electrophysiology and able to run on standard screening platforms.

Q. **Is the lifetime of the cultures important?**

A. Yes, co-culture with glial cells may be vital not only for the longer term health of the neurones but also for their maturation to an adult phenotype.

Q. What part could mathematical modelling play - eg for modelling spread of tauopathy.

A. Only in support of assay development.

Q**. Could successful Phase 1 applicants combine for a Phase 2 application?**

A. Yes if this produced a better application that could meet all the requirements in Phase 2.

Q. **Who owns any IP arising from the project?**

A. Please read the CRACK IT guide for applicants. IP resides with the applicants, but the sponsors may wish to have preferential access rights. The NC3Rs stipulates that the 3Rs benefits must be made available to anyone.

For further information and to be put in contact with the sponsors, please email

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