Challenge 17: Neuratect Surgery Q and As

Q. Should a marketable product be ready after Phase 1 or 2?
A. Phase 2.

Q. Are Sponsors expecting a platform that includes a reader?
A. It needs to be a complete platform to deliver the Challenge brief.

Q. What morphological and structural endpoints are the Sponsors expecting?
A. Applicants need to be creative and proactive with their applications. Sponsors do not have definite requirements, but will be available for discussion and advice around this during Phase 1.

Q. Are you looking to bring together already existing technologies?
A. Yes, starting from scratch may not be feasible in the time frame of this Challenge, so integration of current technologies may be beneficial.

Q. What are the preferences in the type of platform?
A. The Sponsors are open to the type of platform.

Q. Are you able to indicate which specific cell types you are interested in?

A. During Phase 1, it is recommended that there be a focus on the main pathways known to be involved in neurotoxicity and seizure liability. Sponsors will be open for discussion on specific cell types and ideas from applicants during the application process and will provide a list of reference compounds in Phase 1.

Q. How important is it to start to integrate the technologies in Phase 1?
A. It is important to demonstrate integration of the technologies in Phase 1 as it is a key component of this Challenge.

Q. Can you change approach and/or members of team after for the Phase 1 application?
A. Yes, if you think this will present the best proposal (e.g. additional expertise).

Q. How extensive is the compound library offered as in-kind support?
A. It is not yet formally defined, but it will cover true negative /true positive /false negative /false positive compounds detected from conventional studies. Non-clinical and clinical data can also be provided for validation of the model against other gold standards during Phase 2.

Q. What are the criteria for validation in Phase 2, especially as the *in vivo* data does not translate to the clinic?
A. Mixed cell types, spontaneous firing, characterised cell type and maturity. Applicants need to provide evidence after Phase 1 that you can meet Challenge; the exact endpoints will be defined by the type of approach.

Q. Will the Sponsor provide iPSCs?
A. No, these should be provided by the applicants.

Q. Are you more interested in morphological or electrophysiological endpoints?

A. Both.

Q. Is the scope of this Challenge limited to iPSCs?
A. iPSCs are preferred by the Sponsors. Embryonic cells are out of scope.

Q. What electrophysiological data would you require?
A. Basic electrophysiological readouts are required, potentially with cellular surrogates for learning and memory if possible. Analysis of complex networks is not required. Applicants should ensure the platform is of high enough throughput after discussion with the Sponsors.

Q. iPSCs may provide a better model of developmental toxicity early on in their development. Is this in scope?
A. Sponsors would like to recapitulate the situation seen in the current slice culture, so we would need the culture equivalent of 5-6 week old brain (thus mature). Development is not the focus of this Challenge.

Q. Are other electrophysiological readouts acceptable, e.g. voltage sensitive dye?
A. Yes, if they provide equivalent data.

Q. Do Sponsors expect glial cells to be present?
A. Yes, that would be preferable if feasible.

Q. Do applicants need to recapitulate the balance between neuronal cell types to correctly reproduce seizure?
A. Yes, as much as possible, but it is not necessary to analyse complex electrophysiology networks – surrogate recordings of seizure (e.g. from the cortex in animals) will be sufficient.

Q. Do Sponsors want to use a seizure model from diseased iPSCs?
A. No – healthy cellular models only. Seizure states will be induced experimentally.

Q. Do you need 3D culture development in Phase 1?
A. Yes, that would be preferable if feasible.

Q. Is this for short or long term test substance exposure?
A. Short term exposure is a priority. If cultures can survive long enough, we can consider chronic exposure in the future.

Q. Do successful applicants need to validate the assay using animal models?

A. No.

Q. To have a finalised product by the end of Phase 2 is challenging, can it be a prototype?
A. If it is not feasible to finish by the end of Phase 2, plans should be in place to finalise the product to a commercial fit-for-purpose state as soon as possible after. There are no extra funds from the NC3Rs to deliver this.

Q. Can Sponsors suggest some key molecules to test in Phase 1?
A. Sponsors will provide a list of key reference compounds.

Q. What other models do you use right now?
A. For safety pharmacology, we mostly use hippocampal slice culture as our gold standard. *In vivo* models are also used where necessary.

Q. Is the intention to bring this in-house or to outsource a CRO?
A. These studies would probably not be conducted in-house but the business model may differ between Sponsors and other future customers.

Q. Do the measurements need to be simultaneous?
A. There is no specific requirement for simultaneous measurement, but all measurements need to be integrated with the platform.

Q. Who should we email with questions?

A. General questions can be sent to the NC3Rs. Questions regarding a specific challenge can be sent to the Sponsors, but enquiries should be sent to ALL Sponsor parties for a particular Challenge. Please email the NC3Rs to facilitate interaction with the Sponsors at CRACKITenquiries@nc3rs.org.uk.