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Challenge 22: Osteo-Chip Surgery Q&As.

Q. The proposal is quite proscriptive regarding cells that should be used. Would the Sponsors be open to a novel approach which does not use cells?

A. Yes, if the system can take into account the involvement and signalling of the cell types involved in the disease. The rationale for asking for multiple cell types is that the *in vitro* models currently available do not take into account the signalling between cell types during the disease process.

Q. No current cell models recapitulate the osmotic and ionic properties of the joint fluids. What do you want in terms of synovial fluid?

A. Input on the influence of fluidics on the disease is of significant interest. However, due to the potential difficulty is reproducing this in the model, it is a desirable rather than a deliverable.

Q. Why do you ask for 72 hour viability in Phase 1? Many models are amenable to culture for longer time periods.

A. The model should be viable for at least 72 hours. The model should be amenable for screening which will not require long-term culture, and also for longer term mechanistic studies.

Q. Mixed cell cultures such as cell soups have been available for some time. Would the panel consider single cell types?

A. Osteoarthritis (OA) is the interplay between multiple cell types, so this needs to be represented in the model. We are interested in a complex cell culture model; a single cell model is unlikely to fulfil the remit.

Q. What do you mean by 3D architecture? A model could look like the joint, but not behave like a joint. It might be unnecessary to make the model look like a joint.

A. Applicants should take into account that *in vivo* cells are arranged in a specific architecture that permits cell-cell and cell-matrix interaction. Cells in monolayer culture often do not behave as cells do *in vivo*. The model does not need to look like the joint, but the interaction between cells and their native matrix components should be taken into account.

Q. Mechanical loading is very important to OA pathogenesis. Is this really a 'desirable'?

A. The importance of mechanical load should be balanced with the other requirements of the model. Applicants may need to make a choice which to pursue, although the ability to incorporate it would deliver significant scientific benefits.

Q. Is genetic variation important if you want to predict human responses?

A. Yes. OA is a heterogeneous disease. Different people have different initiating pathologies, thus a complex model system that could take this into account would be useful.

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Genetic variation does not need to be present in the Phase 1 proof-of-concept data, but should be considered in Phase 2 plans.

Q. Are you open to microfluidic devices which could be used in parallel to study the different end-points?

A. Yes, as long as the data generated covers multiple aspects of disease pathology.

Q. What would the preferable platform be for outputs and outcome measures?

A. The Sponsors have no strong preference. The platform should be compatible with standard laboratory imaging and/or analytical equipment.

Q. Is there more information on the specific readouts already used at by the Sponsors? For example, which cytokines are considered important?

A. Specific biomarkers will depend on the target being studied. The Sponsors have a multidisciplinary team working on the project, including biomarker experts who will help with the selection of the most appropriate biomarkers in Phase 2.

Q. Six months for Phase 1 is a very short time. What do the Sponsors expect to achieved in this time?

A. Sponsors are expecting proof-of-concept after six months as outlined in the deliverables; proof that your approach has the potential to deliver Phase 2 and data to demonstrate that.

Q. Can we use commercially available cell types?

A. Yes.

Q. Can we use induced pluripotent stem cells (iPSC) which have been differentiated?

A. Yes, provided data on the physiological and pathological relevance of these cells to the human disease is presented.

Q. Commercialisation is a significant component of this Challenge – what is the market size?

A. We anticipate the market to be significant given the investment in the area by private companies and research funders, the unmet clinical need and the concerns surrounding the utility of the animal models.

Q. What is meant by phenotype in the context of the Challenge brief?

A. The phenotype needs to represent as closely as possible the human physiology/disease, including appropriate cell surface markers and disease-relevant functions such as excretion of matrix components, but there is no stipulation to recreate the same 3D structure as the joint. Interaction between different cell types *in vivo* should be accounted for.

Q. If we could make a model that was appropriate for the early inflammatory phase in OA and Rheumatoid Arthritis (RA) as well, would you consider it?

A. OA is the focus of the Challenge and although any applicability to the RA field would be welcome, it should not compromise or detract from the OA deliverables.

Q. Do you envisage a microvascular network is needed to deliver the immune cell components?

A. No, but if you can consider adding the components from the microvasculature and activated endothelium, that would be of scientific benefit.

Q. In current animal models (e.g. the cartilage damage model), several processes are occurring simultaneously, e.g. inflammation, bone remodelling, cartilage remodelling… How do we pick which of these to focus on?

A. We would like as many components as possible present in the model. All applicants will face the same challenge. Applicants must decide which are the priority areas and provide justification for their decision.

Q. Can we have a list of specific outcome measures required?

A. Specific biomarkers and outcomes can be discussed with the Sponsors in preparation for Phase 2. The platforms used should be compatible with common equipment and formats so that the product can be used in a wide range of laboratories.

Q. I have expertise in certain areas, but not in all areas that are required to solve the Challenge. How can I find other expertise?

A. Speak to the NC3Rs office (crackitenquiries@nc3rs.org.uk) and we will do our best to help connect you with the expertise you are seeking. You can also make use of the Challenge-specific LinkedIn pages that have been established.

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. If preferred, please email the NC3Rs to introduce you to the Sponsors at CRACKITenquiries@nc3rs.org.uk.