Title of Challenge

BADIPS – Generating human induced pluripotent stem cells (iPS cells) to study bipolar affective disorder

Background

Mental disorders, including bipolar affective disorder (BAD), are a serious burden on society, including in the UK, and there is a large unmet medical need for novel, more efficacious treatment options (1). Current treatments for BAD originated serendipitously, or secondarily from approaches originally developed to treat schizophrenia or major depression. A key issue is the lack of valid animal models for BAD (2-4), despite the generation of a whole series of genetically altered animals (3). Current animal models have limited impact on the understanding of the disorder and do not predict clinical efficacy of novel treatment options.

Over the last few years, in parallel with other fields, human genetic studies for BAD have been dominated by genome-wide association studies (GWAS), and to a lesser extent by copy-number variant (CNV) studies. These GWAS have identified some polymorphisms but few findings have been reproduced as statistically significant in independent studies (2).

An alternative approach is the use of patient-derived cell models of brain diseases that are relevant and robust enough to produce the large quantities of cells required for molecular and functional analyses, including induced pluripotent stem (iPS) cells (5-8).

3Rs benefits

Current animal models used to study BAD include genetically altered mice and rodent models of schizophrenia or major depression. The latter involves the administration of drugs which cause psychosis in man, or subjecting animals to stress (e.g. maternal deprivation) and are therefore associated with significant welfare concerns. Using iPS cells from BAD patients as screening tools for the development of novel treatment options, it will be possible to reduce the dependence on animal models, improve the predictive validity of the assays, and possibly even make some of the present *in vivo* testing obsolete. Specifically this will include reducing the use of:

- Standard rodent models for novel drug screening, which attempt to mimic some elements of BAD and rely on reference drugs to provide some predictive value. Typically dose-response curves are generated in these models using 7 to 15 animals per treatment concentration;
- Classical behavioural testing in transgenic animals where specific genetic factors derived from GWAS or disease pathway analysis are modified;
- Drug testing in transgenic models;
- *Ex vivo* tissue from transgenic animals.

Need for collaboration

The generation of iPS cells from patient material is a multicentre task, involving clinical scientists who have access to well-defined patient populations, preclinical scientists who can generate and validate the cellular assays, and industrial scientists who will develop these assays to allow high-throughput screening.

Overall objectives

The development of relevant phenotypical high throughput screens for the discovery of new treatments for BAD.

Key deliverables

- Generate viable iPS cells from 5-10 clearly defined BAD patients, ideally carrying polymorphisms in coding regions of risk genes or CNVs that will allow directed investigation of cellular properties as proof of concept;
- Identify phenotypic characteristics of these cells (iPS or differentiated into neurones) that are specifically related to BAD;
- Generate a robust and validated assay suitable for screening in an industrial setting.

Industry sponsors

Janssen and Eli Lilly

In-kind contributions

This will include

- Gene expression profiling;
- High content characterization of iPS derived neurons: antibody labelling and imaging, *in vitro* electrophysiological support;
- Testing human cells and if applicable, cells from rodents carrying mutations in the genes of interest with the aim of building a screening platform;
- Provision of shRNA or siRNA for knock-down of gene expression;
- Access to compound libraries and reference drugs for validation.
- Differentiation of the iPS cell lines into different types of neurons (e.g., GABA, glutamate, dopamine phenotypes);
- Genomic characterization (e.g., mRNA, miRNA, candidate gene expression);
- Functional characterization of the cells using biochemical, electrophysiological and imaging technologies with and without functional genomics and pharmacological tools/probes;
- Testing human cells and if applicable, cells from rodents carrying mutations in the genes of interest with the aim of building a screening platform;
- Access to public domain compounds/reference drugs.

Industry sponsors access to foreground Intellectual Property

Janssen's and Eli Lilly's participation is conditional on a provision entitling Janssen and its Affiliates and Eli Lilly and its Affiliates to use the results of the programme in its research and development (R&D) activities, in the form of a non-exclusive, royalty-free usage right on the results obtained under such project for the purpose of carrying out R&D activities for discovering novel commercial pharmaceuticals.

Duration

Up to three years

Budget

Up to £1 million in total, inclusive of VAT where applicable

Funding model

Although success in the project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise and applications are therefore welcomed from teams forming consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors). More than one such consortium could be funded, particularly if the proposed approaches take substantially different routes.

References

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Keywords

iPS cells, neuronal culture, bipolar affective disorder, assay development, phenotypic screen.