DRGNET – Enabling access to primary human dorsal root ganglion neurones for drug target identification and pharmacological testing

DRGNET aims to:

- Put in place a system whereby high quality and viable dorsal root ganglion neurones can be supplied to both industrial and academic researchers to increase understanding of the human system and facilitate drug target identification and pharmacological testing of novel pain therapeutics.

BACKGROUND

Chronic pain is a common problem affecting approximately 1 in 5 adults across Europe[1]. It has a substantial impact on patients' quality of life and is associated with physical and social disability, as well as psychological distress[2]. Although a variety of analgesic agents are available many patients remain refractory to these treatments because of inadequate pain relief or intolerable side effects. There remains the need for the development of additional treatments with better efficacy and/or toleration profiles.

Pain signalling is transmitted by sensory neurones, a specialised neural population conveying sensory information from the periphery to the central nervous system. The cell bodies of somatic sensory neurones lie out with the spinal column in a series of ganglia, termed dorsal root ganglia (DRG). Key ion channels and receptors expressed in the nociceptive sensory neural population are targets for the development of novel pain therapeutics. The pain field has seen a number of high profile failures through lack of efficacy at Phase II in recent years, and development of more predictive *in vitro* models is key to addressing this.

The pain field suffers from a lack of access to viable human DRG material. Post mortem material is rarely viable enough to allow physiological profiling and no robust immortalised DRG lines have been developed. A few publications have demonstrated the utility of freshly isolated human DRG material for small scale electrophysiological studies[3,4]. Much of the *in vitro* work is carried out on DRG isolated from preclinical species (rodent, dog and non-human primate (NHP)), and the absence of predictive *in vitro* assays results in increased *in vivo* exploratory experimentation in preclinical species. Recent work has aimed to derive human nociceptive neurones from pluripotent stem cells, opening up the possibility of generating induced pluripotent stem (iPS) cells from patients with chronic pain[5]; this work suffers from a lack of comparator studies with human DRG neurones.

A reliable source of human DRG material would allow more physiologically relevant information to be generated in the human sensory neural system for drug target identification and drug

Sponsors
Pfizer, Neusentis, Grünenthal

Budget per project
Phase 1: Up to £100,000 inc. VAT where applicable

Phase 2: Up to £750,000 inc. VAT where applicable

Key words
Human dorsal root ganglion (DRG) pain sensory neurone, human, cell storage and supply

discovery, and the development of more refined stem cell-derived strategies for a higher throughput approach.

3Rs BENEFITS

Access to a reliable source of primary human DRG neurones will lead to several 3Rs benefits:

- Replacement of the use of animal DRGs (rat, mouse, dog, NHP) with human DRGs in basic research and drug development;
- More physiologically relevant *in vitro* models will lead to a reduction in the use of *in vivo* models e.g. scale back of *in vivo* exploratory programmes for target identification and selection triage;
- Better understanding of human DRGs will facilitate the development of iPS cell derived sensory neurons to use in high-throughput screening for candidate selection. Reducing the use of animals on compounds destined to fail later in development.

NEED FOR COLLABORATION

The project will require access to a regular source of freshly isolated human DRG material, infrastructure for tracking and shipment of this material, and storage solutions for cryopreserved materials. It is also possible that an applicant may wish to use the material to carry out fee-for-service research. This will involve clinical scientists with access to donors, managers for shipment logistics, and preclinical scientists to carry out cryopreservation and any fee-for-service work required.

OVERALL AIM

To put in place a system whereby high quality and viable dorsal root ganglion neurones can be supplied to both industrial and academic researchers to increase understanding of the human system and facilitate drug target identification and pharmacological testing of novel pain therapeutics.

KEY DELIVERABLES

Phase 1

- Demonstrate the ability to provide a consistent supply of human DRG material which is ethically sourced, viable and suitable for physiological and pharmacological testing;
- This will include consideration of (i) where the primary cells would be obtained from, i.e. transplant clinic networks, and (ii) the training requirements for surgeons to harvest the best quality DRGs.

Phase 2

- The supply would need to meet varying research demands depending on the platforms used. For electrophysiology, 1-2 DRGs per week would be sufficient; this would increase for transcript profiling or plate based pharmacology;
- A key component of delivery will be to evaluate the possibility of shipping cells either as viable material at ambient temperature or as frozen cryopreserved stocks;
- Costing of material must not be prohibitively expensive. A tiered costing system for access to the resource by multiple sectors/users should be considered with an estimated maximum of £650 per DRG or per microwell plate's worth of cryopreserved cells;
- There must be a sustainable business model to allow supply to continue after seed funding is exhausted;

- The Challenge also considers long term and scalable solutions to replace the human DRGs, such as development and validation of pluripotent stem cell-derived sources for human sensory neurones as a next horizon for pain research.

IN-KIND CONTRIBUTIONS

Phase 1

- Advice and guidance on industry requirements for harvested DRGs and what criteria are used for assessing cell viability and suitability for physiological and pharmacological testing.

Phase 2

- Guarantee of minimum spend for 2-3 years;
- Optimisation of dissociation and cryopreservation protocols;
    - Molecular profiling of DRGs;
    - Comparison of heterogeneity between DRGs from individual humans;
    - Comparison of human DRG with pluripotent stem cell derived sensory neurones;
- Comparison of animal and human DRGs;
    - Single cell sorting and transcript analysis;
    - Microarray studies;
    - Electrophysiology.

ETHICAL APPROVAL AND CONSENT

Ethical approval and consent forms must be drafted in such a way as to allow industrial partners to freely use cells supplied for research and development purposes, including the testing of proprietary compounds for discovering novel commercial pharmaceuticals.

REFERENCES

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