both keep the multipotency after 6 passages and the potential to differentiate to mature region specific neurons.

In conclusion, here we show that hfNSCs can be expanded in vitro and may be suitable for cell therapy in HD.

Clinical therapeutics

M19 SERTOLI CELL TRANSPLANT: NEW HOPE FOR THE TREATMENT OF HUNTINGTON DISEASE (HD)

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Introduction Huntington disease (HD) is a neurodegenerative disorder characterised by progressive worsening of behavioural, cognitive and motor function. The disease-causing mutation is an expanded CAG repeat in the huntigtin gene. Although rapid advancing basic and translational research has identified numerous potential targets for treating HD, no definitive cure is currently available. Promising research on alternative therapeutic approaches, however, offers new hope. Experimental evidence indicates that testis-derived Sertoli cells (SCs), which have been demonstrated to play a critical role in different pathophysiological activities, have the potential to be a very useful tool for chronic neurodegenerative conditions.

Objective To test the ability of SCs to secrete molecules with neuroprotective properties and whether their transplantation into HD R6/2 mice may represent an effective strategy for developing therapies.

Methods In vitro experiments were carried out in mouse striatal-derived cells with 111 CAG repeat (STHdh111/111), cultured in apoptotic conditions, in presence or absence of conditioned medium from SCs. Cell survival was evaluated by Annexin V staining. In vivo experiments were performed on transgenic R6/2 mice and wild type littermates. The effect of SCs transplantation on motor function and longevity was assessed by behavioural testing and survival analysis, respectively.

Results Coherently with in vitro studies that highlighted protection of cells from apoptosis, in vivo studies showed that SCs transplantation efficiently ameliorated the overall motor function in R6/2 mice and significantly prolonged lifespan in the same mice.

Conclusions The beneficial effects of SCs transplantation in HD models provide new perspectives for innovative therapies in HD, however further studies are warranted.

M20 ACTIVATION OF THE TRKB RECEPTOR PATHWAY USING A NOVEL MONOCLONAL ANTIBODY AGONIST: IMPLICATIONS FOR THE TREATMENT OF HUNTINGTON’S DISEASE

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Introduction Huntington disease is a debilitating neurodegenerative disease marked by a trinucleotide repeat expansion in the huntingtin gene (HTT) that might lead to production of a pathogenic mutant huntingtin protein (mHTT). Recent evidence suggests that alterations in neurotrophin tyrosine kinase receptor signalling pathways contribute to HD pathophysiology. Brain-derived neurotrophic factor (BDNF)-mediated activation of the tyrosine kinase B (TrkB) receptor is a critical component involved in the survival, differentiation and synaptic plasticity of striatal neurons. Reduced levels of BDNF have been previously reported to be observed in both HD post mortem brain tissue and HD mouse models. Furthermore, mHTT has been shown to reduce levels of BDNF in the striatum by inhibiting its gene expression and cortico-striatal trafficking.

Aims In this study, we explore the capacity of novel mouse TrkB agonistic monoclonal antibodies (mAb TrkB agonist) to activate the TrkB receptor signalling pathway in vitro.

Methods The mAb TrkB agonists were tested in vitro to confirm receptor selectivity, efficient binding affinity and functional activity. Subsequently, wild type mice received intrastriatal bolus injections of mAb TrkB agonist at 6 weeks of age and were sacrificed at four different time points post injection.

Results At 30 min post injection, a significant increase in the phosphorylation of TrkB was observed in striatal neurons of mice treated with the mAb TrkB agonist when compared to vehicle treated and non-treated animals. At 4 h post injection, the levels of TrkB phosphorylation were returned to baseline levels. Quantitative western blots were also performed as an orthogonal method to confirm immunohistochemical results.

Overall, our findings demonstrate the functional activity of mAb TrkB agonist antibodies in the CNS and establish the potential of an immuno-therapeutic approach for restoring aberrant BDNF-TrkB signalling activity in the HD brain.

Clinical therapeutics

N01 CELL TRANSPLANTATION IN HUNTINGTON’S DISEASE

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Introduction Cell transplantation is becoming a viable therapy for patients with Huntington’s disease (HD). Studies using rodent models of HD have identified a need for extended behavioural training to allow the recipient to ‘learn to use the graft’. Thus, after intra-striatal grafting of foetal tissue, striatally-dependent behaviours need to be re-established through targeted training.

Aims

• To determine the extent to which cell transplantation can alleviate a range of cognitive deficits in rodent models of HD, and to identify the optimal parameters for successful alleviation of deficits.

• To develop a functional motor assessment in HD patients, that sensitively capture improvements in motor function that manifest post-transplantation.

Method Rats will be pre-trained on a cognitive operant task that relies on the medial striatum. After receiving bilateral striatal lesions, a subset will be grafted with foetal ganglionic eminence. Thereafter, rats will be re-tested on the task at either 2 or 12 weeks post-graft to determine the optimal time to commence cognitive training.