G Experimental therapeutics: clinical

G.1 THE ROAD TO DELIVERY OF HUMAN EMBRYO STEM CELL-BASED THERAPIES

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Realising the therapeutic promise of human embryo stem cells (hESC) necessitates overcoming diverse challenges. This begins with meeting the legal and ethical challenges of procuring embryos. Next, the efficiency of in-vitro culture systems supporting cells must be improved using reagents whose specification complies with regulatory standards. This is followed by qualification of resulting cells and assessment of their biosafety both in relation to the prospective transplant recipient and the community at large. Complicating the address of these challenges are constantly evolving and internationally variant regulatory standards that have the capacity to negate the utility of cells for emerging therapies before clinical trials are even begun.

To address these challenges Roslin Cells Ltd was established in 2006 as a not-for-profit company owned by the University of Edinburgh, the Scottish National Blood Transfusion Service and the Roslin Institute. It is core funded by Scottish Enterprise, which recognised the market failure caused by a lack of industrial investment in a promising yet unproved technology and limited research council support for translational research. Similarly to other UK centres attempting to derive hESC, Roslin Cells Ltd is licensed by the Human Fertilisation and Embryology Authority. In addition it is the first centre to be licensed by the Human Tissue Authority for the processing, testing, storage, distribution and export/import of embryos and stem cells intended for human application. To date Roslin Cells Ltd has isolated five new research grade hESC, including one from a clinically failed egg created in the course of assisted conception that otherwise would have been discarded. Roslin Cells Ltd has now begun to isolate clinical grade hESC under increasingly defined culture conditions that will safeguard against contamination with known or unknown pathogens. Clinical evaluation of the resulting cells will still require development of methods to differentiate cells with specialised function required to treat different types of disease, as well as the characterisation of such cells in animal models for their biosafety. Although this will still require further investment of time and resources before clinical benefits can be had, the first important step of creating a resource of clinically suitable cells is underway.

G.2 NEURAL TRANSPLANTATION IN HUNTINGTON'S DISEASE: FOLLOW-UP ASSESSMENT IN NINE PATIENTS

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Background and Aims: At the University of Florence, during the past 2 years, we have performed human fetal striatum transplantations (HFST) in nine patients affected by Huntington's disease (HD), according to the accepted protocol. We present the main biological and clinical results.

Methods: Standard procedure (Bachoud-Lévy, 2000) was applied to the first six interventions, the remaining grafts were performed by a double approach refinement. Patients were assessed with the Unified Huntington's Disease Rating Scale, neuropsychological and psychiatric battery: twice in the year before the graft and yearly after the graft. Furthermore, patients underwent regular magnetic resonance imaging/18F-fluorodeoxyglucose positron emission tomography/iodobenzamide single-photon emission computed tomography examinations.

Results: Nine patients underwent HFST: two patients reached 2 years of follow-up, four patients one year, two patients 6 months and one patient 3 weeks. The gender ratio of the patients was three women/five men, mean age was 47 years (±8, 86 SD), the age at disease onset was 34.25 years (±10, 18 SD), mean duration of illness was 13 years (±6, 93 SD), mean CAG repeats 49.25 (±5, 97 SD). Three patients showed a conspicuous growth of the graft on one side (without signs or symptoms of neurological deterioration), within a period of 7–9 months after grafts, followed by a stabilisation of growth. Our clinical findings are very similar to those presented by Bachoud-Lévi; in particular, we noticed an improvement in the cognitive domain, whereas we did not find a striking improvement in motor symptomatology. In the three patients who showed graft growth, we did not observe, so far, any positive correlations in the clinical outcome.

Conclusions: The evaluation of HFST as a useful therapeutic tool is still under debate, as well as our knowledge of the capacity of fetal tissue to create new connections with an adult neurological structure affected by degenerative disorders.

G.3 BILATERAL STIMULATION OF THE GLOBUS PALLIDUS INTERNUS TO TREAT CHOREA AND AXIAL DYSTONIA IN HUNTINGTON'S DISEASE: A CASE REPORT

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Background: Huntington's disease (HD) produces motor abnormalities that are poorly responsive to medical therapy. Deep brain stimulation (DBS) may offer a treatment option for afflicted patients but its role in the management of HD remains unclear.

Case History: A 42-year-old man with a diagnosis of HD for the past 4 years, with predominant axial dystonia in the neck, severe chorea in the upper extremities and with severe impairment of gate was enrolled for surgery. The surgical procedure was similar to that performed in patients with dystonia. The surgery was carried out under local anaesthesia. The globus pallidus target was determined by magnetic resonance imaging, computed tomography and unit cell recordings. The pallidal target was 3 mm anterior to the mid-commissural plane, 20 mm lateral to the midline and 4 mm below the intercommissural line. The optic tract determined the lower boundary of the globus pallidus. It was identified by phosphenes seen by the patient during stimulation. The implanted electrode was a DBS model 3387 (Medtronic, Minneapolis, Minnesota, USA). DBS parameters were: 2.8 V, 120 ms, 180 Hz, monopolar.

Conclusions: Bilateral pallidal stimulation produced a dramatic reduction in choreathetoid and dystonic movements and an overall improvement in gait. The cognitive profile showed no deterioration. The patient reported better quality of life. The immediate post-surgical results were promising but too early to draw conclusions.

G.4 A CASE OF ARIPIPRAZOLE-INDUCED CHOREA

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Background: Aripiprazole is a second-generation antipsychotic with the property of a dopamine-2 receptor partial agonist, often used as a second-line agent, raising the question of an optimised therapeutic switch after prolonged treatment with typical/atypical neuroleptics.
Case report: A 66-year-old woman had a 20-year history of psychiatric disease treated with various antipsychotics (haloperidol, risperidone). In 2003, after shifting from haloperidol to aripiprazole, she presented with facial dyskinesias. Afterwards dyskinesias diffused to all the body regions and after a few months she had generalised chorea. In 2006, aripiprazole was discontinued and olanzapine was introduced, with a dramatic increase of choreic dyskinesias. At that point the patient was referred to our hospital. The neurological examination revealed: orolingual dyskinesias, generalised chorea, gait unsteadiness, motor impersistence, no apparent cognitive dysfunction. She had no family history of movement disorders. Neuroimaging, laboratory tests and genetic testing revealed no other possible pathogenetic causes of chorea. Olanzapine was discontinued and tetrabenazine was titrated up to 75 mg a day, with a gradual improvement of chorea.
Conclusions: The dyskinesias started after the exposure to aripiprazole. Only a few cases of aripiprazole-induced movement disorders have been reported so far; in one case aripiprazole was reported to improve tardive dyskinesias. Tetrabenazine was effective in treating chorea. Previous exposure of this patient to neuroleptics would increase the basal ganglia responsiveness and favour the agonist profile of aripiprazole. We hypothesise that chronic administration of neuroleptics may lead to dopamine-2 receptor hypersensitivity in the nigrostriatal pathway. This would promote the activation of dopamine-2 receptors by aripiprazole, explaining the emergence of dyskinesias. Tetrabenazine was confirmed to be effective in treating chorea.

G.5 BUPROPION: FIRST EXPERIENCE IN HUNTINGTON'S DISEASE

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Background: Depression and especially apathy are central clinical features in Huntington's disease (HD). Apart from the dopaminergic antidepressant effect, the biochemical structure of bupropion resembles amphetamine structures, resulting in an improvement of apathy.
Methods: Seven patients with depression and apathy with genetically confirmed HD (three men, four women; mean age 51.4 ± 13.2 years) were treated with bupropione 150–300 mg/day. The extent of depression was assessed by the Hamilton Depression Rating Scale (HDRS). Neurological status was documented by the Unified Huntington's Disease Rating Scales (UHDRS; subscales motor score (MS), independence scale (IS), total functional capacity (TFC)). Ratings were performed initially and in a follow-up investigation 6 months later or at the time of discontinuation of medication.
Results: The mean age of motor onset was 44.4 ± 12.6 years; psychiatric onset was 42.8 ± 14.7 years (n = 6). Initial mean scores for UHDRS were: MS 40.1 ± 24.5; IS 60.0 ± 8.2; TFC 7.1 ± 2.2; HDRS was 19.1 ± 10.7. Due to side effects or the absence of therapeutic effects four of seven patients terminated treatment before maturity. Three patients stopped treatment after several days because of increased irritability (one 300 mg/day and two 150 mg/day). One patient on 150 mg/day stopped treatment after 3 months due to non-response. Of three remaining patients (two 150 mg/day, one 300 mg/day) MS was 54.7 ± 24.5, chorea, IS and TFC were unchanged, whereas HDRS improved to 8.3 ± 4.9. As the initial HDRS for these patients had been 15.3 ± 10.1, the improvement definitely depends on the one patient at 300 mg/day who ameliorated from 26 to 6 with less apathy.
Conclusions: In single HD patients bupropion may be an effective antidepressant. However, we had many non-responders. This effect seems to be dose dependent. In addition, we observed increased irritability in some patients. As this is only an initial case series we emphasise that further research needs to be done on this compound in HD.