Clinical translation of stem cell therapies for Huntington's Disease

Rosser AE, Busse ME, Gray WP, Aron Badin R, Perrier AL, Wheelock V, Cozzi E, Perpiña U, Salado-Manzano, Mills LJ, Drew C, Goldman SA, Canals JM, Thompson LM on behalf of *Stem Cells for Huntington's Disease (SC4HD) and* the *EHDN Advanced Therapies Working Group*

Background

- The underpinning concept of regenerative medicine is **restoration of structure and function**.
- This can be achieved through several approaches, including implantation of cells to either provide **support** for vulnerable host cells or to **integrate and adopt the function of cells lost to the disease process**.
- There is a long history of primary foetal striatal transplantation in HD demonstrating that foetal striatal progenitors can restore elements of striatal circuitry in rodent models of HD, accompanied by recovery of function, and two pilot human proof of concept studies demonstrating functional recovery.
- Foetal cells are scarce and very difficult to quality control, so there has been a major effort to identify stem cell derived donor products from human embryonic stem cells, induced pluripotent stem cells and foetal derived neural stem cells.
- There is a growing body of published preclinical efficacy data following transplantation of precursor cells and glial progenitor cells in HD animal models.
- Thus, HD represents an excellent prospect for regenerative medicine, but there **are multiple challenges along the translational pipeline**, many of which are common across diseases and pertinent to multiple donor cell types.

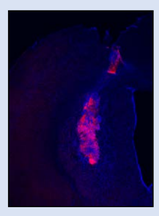
Establishing global platforms for addressing clinical translation challenges

To start addressing translational challenges, we established two international platforms, **stem cells for HD (SC4HD)** and the **EHDN Advanced Therapies Working Group**, and a related task force - the **Surgical Delivery Task Force**.

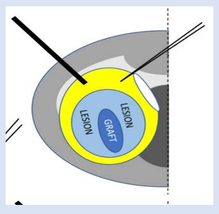
The geographical distribution of the members involved in SC4HD consortium and Advanced Therapies Working Group. 28 members are distributed within 10 countries from 3 continents.

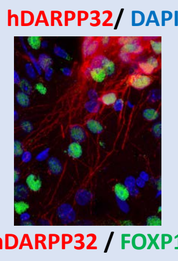
LEFT: 50 face to face attendees of the first SC4HD meeting at the Beckman Center for National Academies of Science, Engineering and Medicine and UC Irvine Stem Cell Research Center in 2018.

RIGHT: 26 researchers attended a joint meeting of the SC4HD consortium and the EHDN Advanced Therapies Working group in the NH Collection Podium Hotel, in 2019.

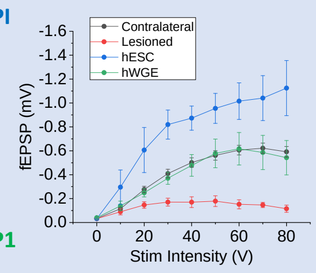


hDARPP32/ DAPI



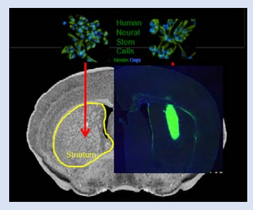


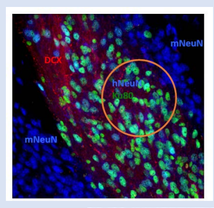
hDARPP32 / FOXP1

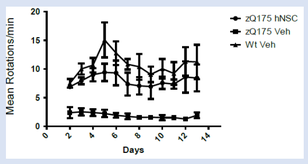


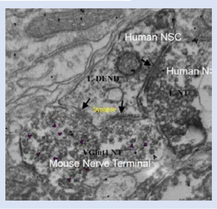
Repair-HD consortium: hESC derived MSNs protocols based on protocols Arber et al Dev.2015 & Nicoleau et al Stem cells 2013. hESC grafts max fEPSPs show significant improvement compared to lesion only condition (F=6.671, P<0.00001).

Examples of preclinical studies demonstrating efficacy of stem cell derived products for cell therapy in HD

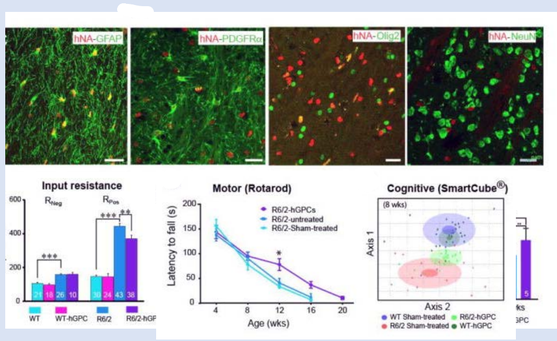








CIRM funded hNSC intrastriatal transplantation. Transplanted ESI-017 hNSCs survive, differentiate in vivo, rescue behavior and form synaptic contacts. Protocols based on Reidling et al, Stem Cell Reports 2018.



Glia are affected early in the pathogenic course of HD -
Goldman SA. Progenitor cell-based treatment of glial disease. Prog Brain Res. 2017;231:165-189.

Challenges to clinical translation

We have identified eight key challenges that need to be addressed in order to optimise clinical translation of cell therapies in HD. We plan to address these through activities of SC4HD/EHDN Advanced Therapies working group and the Surgical Task Force.

1: Defining principles that can be used to guide decisions to advance a potential stem cell therapy towards a first-in-man trial: including identifying the proposed biological mechanism underlylng activity of the cell product, the optimal preclinical models for assessing efficacy and establishing key readouts that define the preclinical data sufficient to consider the candidate as a serious therapeutic medicinal product.

2: Cell manufacturing, scale-up, safety and compliance of cell product for human application: Human stem cells can be guided to differentiate into neural or glial progenitors with a range of potential differentiation capabilities. This process must be optimised to ensure that cell products possess the desired characteristics. Optimized protocols need to be GMP standardized for manufacturing.

3: When to consider the use of large animal models: Preclinical assessment of safety and efficacy studies may require the use of large animal models with larger brain sizes and similar anatomical organization to that of humans. Such models may also model elements of HD pathology.

4: How can we optimally deliver cells to the brain? There are no CE marked devices that have been optimised for cell delivery and neurosurgical procedures have not been defined or explored in detail.

5 Designing clinical trials in practice: A major challenge is conforming to regulatory standards at the same time as ensuring efficient design principles. The use of placebo is important , but especially challenging for early stage surgical studies.

6: Developing a framework for patient selection and follow up in cell therapies studies: Patient selection criteria will affect the safety of targeting and delivery of cellular products. Disease stage should account for therapeutic mechanism(s) and the safety and precision of neurosurgical delivery

7. Post transplantation management to maximize graft survival and integration/immunosuppression: This includes designing immunosuppression, stem cell lines selection or genetic engineering to maximise graft survival and integration, and the importance of long term follow-up to measure repair beyond replacement, including clinical outcomes measure and pharmacovigilance of patients treated with cell-based product.

References:

- SC4HD Consortium. Stem Cells for Huntington's Disease (SC4HD): An International Consortium to Facilitate Stem Cell-Based Therapy for Huntington's Disease. JHD. 2021;10(2):221-226. PMID: 33814456
- Rosser AE et al. Cell Therapy for Huntington's Disease: Learning from Failure. Mov Disord. 2021 36(3):787-788. PMID: 33749919.
- Bachoud-Lévi AC et al Cell therapy in Huntington's disease: Taking stock of past studies to move the field forward. Stem Cells. 2021 39(2):144-155. PMID: 33176057.