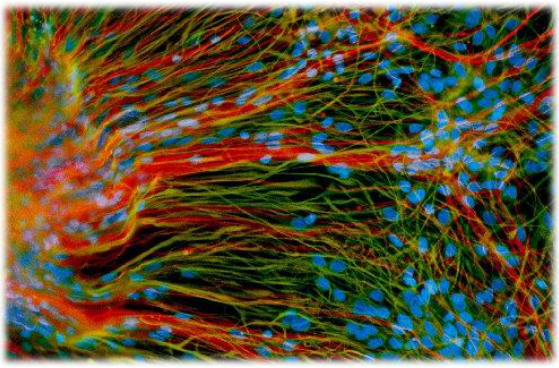

Precursor neural cells grow in a lab dish, generating mature neurons (red) and glial cells (green) (Courtesy Su-Chun Zhang, University of Wisconsin-Madison).

Stem cell research is proceeding with hope and caution

Stem cell research is frequently in the news and the HD community is following closely to see if treatments will result. This could happen in several ways. An earlier update reported on the development of a line of stem cells with the Huntington's Disease gene. http://www.hdsa.org/images/content/1/1/11500.pdf These cells can be used to model the disease to gain new insights into targets for treatments. In addition, they can be used in high throughput assays to screen potential treatments.

Stem cells might be used in treating the disease. One possibility is to stimulate the brain's own production of stem cells. Dr. Steven Goldman and colleagues used a viral vector to introduce genes for factors BDNF and noggin into the brains of the R6/2 mice. New neurons were generated, motor performance improved, and survival time increased. (To read more follow these HD Lighthouse links:
http://hdlighthouse.org/research/bdnf/updates/1255bdnf.php
http://hdlighthouse.org/showUpdate.php?p_articleNumber=497)

Another possibility is that stem cells could be introduced into the brain with the hope that they would replace dead and dysfunctional cells. Stem cells might serve as a primary treatment or they might be used to restore brain cells lost in Huntington's disease following a treatment or combination of treatments that halt progression. If RNA interference is found to be safe and effective, for example, it might be followed by stem cell treatment for those in the later stages of the disease.

Types of stem cells

One issue which is not yet clear is which type of stem cell would be most appropriate for treating a neurodegenerative disorder if researchers move forward with clinical trials of donor stem cell lines. Research demonstrating efficacy and safety will be critical and ethical and public policy considerations may have an influence as well.

Stem cells are undifferentiated cells, cells which have not yet developed into the specialized cells of the human body such as the neurons and glia of the brain or blood or skin cells. They can replicate indefinitely.

Embryonic stem cells are harvested from embryos in the earliest stage of development. Researchers use embryos that were created for in vitro fertilization but were not needed. They have the capacity to become any type of human cell.

Somatic stem cells are tissue specific. They are undifferentiated but can only develop into the cells needed in that area of the body. One example is fetal neural stem cells which are harvested from the brains of aborted fetuses. Adult stem cells are harvested from volunteers. For example, adult blood-forming stem cells have been harvested from the bone marrow of volunteers and transplanted to patients for decades.

Recently, researchers have been able to reprogram adult cells to become stem cells again, essentially turning back the clock. The new induced pluripotent stem cell (iPS) technique involves the use of either certain types of skin cells called fibroblasts or certain types of bone marrow cells. The cells are transfected with four genes inserted into a viral vector. The four genes reprogram the cells to become stem cells with the potential to become any cell in the body. The technique used has rendered the cells unsuitable for donation. However, researchers at Harvard are using a different viral vector which appears to avoid the problem (see link below).

Challenges and risks

As promising as stem cell research appears to be, there are a number of challenges to be met before stem cells could become a safe and effective therapy. Pre-clinical studies are needed to demonstrate efficacy and safety, but researchers are aware that animal models do not always predict how humans will respond to the same intervention. One major concern is whether the use of stem cells would cause the development of cancerous tumors over time.

The International Society for Stem Cell Research has identified a number of areas that need to be addressed in their Guidelines for the Clinical Translation of Stem Cell Research which were developed by "stem cell researchers, clinicians, ethicists and regulatory officials in thirteen countries." (see link below). Thirty-nine recommendations address areas such as the need to demonstrate efficacy and safety in preclinical studies, for peer review of research, for independent review and oversight of proposed trials, the communication of potential risks and benefits and obtaining informed consent, and for frank reporting of failures and adverse events.

Offshore stem cell clinics

In the last few years, stem cell clinics have been established in China, the Soviet Union, and other countries and are being marketed to patients through the Internet. Is it possible that their researchers have somehow leapfrogged over those from the United States and other countries where the researchers are still involved in preclinical research and come up with safe and effective treatments? They provide no scientific evidence to suggest that this is so.

An article which appeared in the journal Cell Stem Cell reviewed the claims on the 19 websites the authors were able to find. Sixteen of these websites offered treatment for neurological problems. The authors found that the websites inaccurately portrayed the treatments as "safe and effective for a broad range of diseases in the context of routine clinical use." Potential side effects were downplayed and testimonials were presented instead of citations to research articles in reputable scientific journals. The treatments were expensive, averaging around $25,000. The authors searched the literature but could not find peer-reviewed research which supported the treatments.

The International Society for Stem Cell Research has expressed concerns about these clinics:

> Numerous clinics around the world are exploiting patients' hopes by purporting to offer new and effective stem cell therapies for seriously ill patients, typically for large sums of money and without credible scientific rationale, transparency, oversight, or patient protections. The ISSCR is deeply concerned about the potential physical, psychological, and financial harm to those who pursue unproven stem cell 'therapies' and the general lack of scientific transparency and professional accountability of those engaged in these activities.

A disturbing case report

An article has been published in PLoS Medicine which reports on the case of a young Israeli boy with ataxia telangiectasis , a neurodegenerative disorder. Against the advice of his doctors, his parents took him to a Russian stem cell clinic where beginning in 2001 he received several injections of human fetal neural stem cells into the brain and the surrounding fluid. No improvement was seen in his condition. In 2005 he complained of headaches and an MRI revealed tumors in the brain and on the spinal cord. The tumors in the brain were slow growing and have not been removed but the growth on the spinal cord was removed.

The tumor was analyzed and it contained DNA from at least two donors, one of whom was female. This shows that the tumor was not something that the boy might have developed anyway but was caused by the stem cell injections.

Clinical trials

If ongoing preclinical research suggests that some form of stem cell treatments are likely to be safe and effective, researchers may proceed to clinical trials. The progress to date has been exciting and hopeful but challenges remain. When trials do begin they will involve patient volunteers who are fully informed about the trial and the risks and carefully monitored throughout the trial and afterwards. Safety data will be continually analyzed and patients will not be charged for their participation.

At this time, if a clinic is charging for unproven ‘treatments' or trials, promising ‘cures', and citing testimonials rather than solid scientific research and if details about procedures and ‘formulas' are clouded in secrecy, potential patients should recognize that these are warning signs that the clinic or trial is *not* legitimate.

Dr. Thompson's letter : http://www.hdsa.org/images/content/1/1/11844.pdf
ISSCR press release on the case report :
http://www.hdsa.org/images/content/1/1/11848.pdf
ISSCR patient handbook : http://www.hdsa.org/images/content/1/1/11845.pdf

References and links:

Ninette Amariglio, Abraham Hirschberg, Bernd W. Scheithausen, Yoram Cohen, Ron Loewenthal, Luba Trakhtenbrot, Nurit Paz, Maya Koren-Michowitz, Dalia Waldman, Leonor Leider-Trajo, Amos Toren,Shlomi Constanti, and Gideon Rechavi. **“Donor Derived Brain Tumor Following Neural Cell Transplantation in an Ataxia Telangiectasia Patient.”** PLos Medicine Vol 6:2 (February 2009): 221-31.

Darren Lau, Ubaka Ogbogu, Benjamin Taylor, Tania Stafinski, Devidas Menon, and Timothy Caufield. **“Stem Cell Clinics Online: The Direct-to-Consumer Portrayal of Stem Cell Medicine.”** Cell Stem Cell Vol. 3 (December 4, 2008):591-4.
http://download.cell.com/cell-stem-cell/pdf/PIIS1934590908005730.pdf?intermediate=true

International Society for Stem Cell Research. **Guidelines for the Clinical Translation of Stem Cell Research.** December 3, 2008.
http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf

MIT, **“Stem Cells without Side Effects.”** Technology Review September 25. 2008.
http://www.technologyreview.com/Biotech/21430/

National Institute of Health. **“Stem Cell Basics.”**
http://stemcells.nih.gov/info/basics/basics4.asp

- *Marsha L. Miller. Ph.D. March 30 , 2009.*