STATE OF THE FIELD OF STEM CELL THERAPIES :

PATIENTS SUFFER WHEN SCIENCE AND GOOD MEDICINE COLLIDE

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Stem cells for physiologic regeneration are found in almost every organ of the adult body. While regenerative cells are broadly classified as 'stem cells' they can be further divided by their 'potency' which describes the potential they possess to become differentiated functioning cells. Adult stem cells exhibit a wide range of potency, from cells capable of differentiating into only one type of functioning cell, uni-potent cells such as skeletal myoblasts, to cells capable of differentiating into cells of all three germ layers, pluripotent cells such as VSELs (adult very small embryonic like stem cells [(1)]) which are being developed clinically by a company called NeoStem. Adult stem cells have been isolated from the blood, bone marrow, spleen, liver, pancreas, heart, skin, fat tissue, nasal olfactory tissue and other organs.

For regenerative medicine purposes, whenever possible, the preferred source of stem cells will be the patients' own endogenous stem cells because these cells possess no risk of immune rejection nor do they require banking or other supply chain infrastructure. Additionally, use of autologous stem cells has an economic advantage, as the costs of these treatments are lower than patented stem cell technologies. However, the properties of autologous stem cells that make them economically advantageous for the patient who has to pay for the treatment, also create obstacles to clinical development of these stem cells. Since a patient's own stem cells cannot be patented, clinical trial progress relies on public funding, including private donors, foundations, and governmental organizations. In the absence of public funding for autologous adult stem cell development, clinicians must devise proprietary isolation methods or other proprietary procedures that allow them to recoup clinical trial to pay for the development of these therapies.

The first regulatory approved autologous stem cell therapy milestone was met in July 2011 when Korea approved Hearticellgram-AMI for heart attack [(2)], following 6 years of clinical trials and demonstration of a substantial improvement in heart function with the therapy. This should have been important breaking news, however no mainstream news covered this milestone event. Similar adult autologous stem cell therapy clinical trials for heart attack are in Phase III clinical trials in Germany and close to approval. In the US, adult autologous stem cells for heart attack did not complete Ph I trials until September 2010, making the US at least 5 years behind the rest of the world in bringing these therapies to patients.

World wide, as entered into the US NIH clinical trials database, adult autologous stem cells are being tested for over 23 diseases including ; stroke, critical limb ischemia, lupus, multiple sclerosis, heart failure, types I and II diabetes, spinal cord injury, sickle cell anemia, non-healing bone fractures, retinitis, cirrhosis, epilepsy, Crohn's Disease, Sjogren's Syndrome, Parkinson's, cartilage repair, and chemical induced blindness[(3)].

Adult autologous stem cells have been used clinically for post-radiation or chemotherapy recovery for decades, and are classified for these cancer based indications by most regulatory agencies as 'minimally modified'. It was not until the mid- to late-1990s that the medicinal properties of adult stem cells beyond hematopoietic recovery were discovered. Those discoveries led rapidly to clinical trial investigations, with Germany predominantly leading and forging the way. Curiously, the US and UK, where embryonic stem cell research is legal and favored by academic scientists, lagged behind in pursuing adult stem cell therapies. As of 30 August 2011, only 39% of the registered clinical trials for autologous adult stem cell therapy for novel disease treatments are in the US, in contrast to 70% of the registered clinical trials for autologous adult stem cell therapy for cancer and conventional hematological diseases. The US leads the world in conducting stem cell clinical trials for cancer patients, but lags behind the world for novel uses of adult stem cells. NIH funding follows a similar pattern; they are funding only 25% of the trials for autologous adult stem cell therapy for novel disease treatments but 50% of the trials in cancer related therapies[4] . This might lead one to conclude that cancer is more prevalent in the US than diabetes, multiple sclerosis, heart attack, heart failure, lupus, critical limb ischemia, blindness, etc. However, the NIH and NCI statistics demonstrate that in 2008 overall US cancer incidence was 463.37 per 100,000 and prevalence was 2.76%, and of that number hematological malignancy incidence was 50.85 per 100,000[5]. Comparatively, considering only three of the diseases for which adult stem cell therapies are being tested clinically - stroke, heart failure and acute myocardial infarction – US 2007 prevalence dwarfed cancer prevalence at 8.1% [6].

While patients in the US and UK have suffered because adult stem cell trials in those countries have not been vigorously pursued, animals in the US have benefited tremendously from adult stem cell therapies[7]. Animals treated with stem cells have made the US news, such as Lex the dog treated for shrapnel injuries or Eli the quadriplegic donkey who now walks again. For veterinary purposes, the adult stem cells are taken from bone marrow or from fat tissue in the animal, cleaned up, and then injected directly into a damaged joint or to a fractured bone or to a damaged kidney or liver. The price tag for veterinary adult stem cell therapies runs between $1800 to $5000 US dollars. For instance, rather than a $12,000 joint replacement, Labradors can receive $1800 stem cell therapy with equivalent outcomes to the invasive joint replacement surgeries[8]. If one asked a veterinarian why they were using adult rather than animal embryonic stem cells for therapy the reply would include the following justifications : embryonic stem cell treatments might require lifelong immunosuppression with a resulting risk of hypertension, diabetes and osteoporosis from the immunosuppressants [9]; ES cells have the danger of forming tumors[10] if they are not rejected by an immune response; ES cells would be too expensive. A veterinarian might say it doesn't seem practical to use embryonic stem cells when we can effectively, safely and affordably treat these animals with adult stem cells.

Desperate for adult stem cell treatments and tired of being deprived of these therapies in their own country, US citizens have created an industry of 'stem cell tourism' and one high profile personality even recently underwent non-FDA approved adult stem cell therapy within the US. Governor Rick Perry of Texas, a Presidential candidate for the 2012 US elections, was treated with his own stem cells taken from fat tissue during a recent surgery to correct a bad back. In the stem cell tourism side, New York Yankees pitcher Bartolo Colon traveled to the Dominican Republic for adult stem cell therapy that has returned him to the mound. Controversy has arisen about the decisions of personalities like Rick Perry and Bartolo Colon to receive adult stem cell therapy [11]. Critics question

the quality of treatment received in the 'stem cell tourism' facilities or the wisdom of obtaining non-FDA approved therapies. The critics are, almost universally, embryonic stem cell proponents and their objections hijack the true nature of the questions we should all be asking. The real issue is why aren't adult stem cell therapies available in the US, UK and other European countries? Why have regulatory agencies such as the FDA put up roadblocks to the development of autologous adult stem cell therapies by denying these therapies the 'minimally modified' classification that is given to the same methods and procedures when the autologous adult stem cells are used for cancer patients?

What is the true agenda of embryonic stem cell proponents? Embryonic stem cells were first isolated from mice in the late 1970s. They were isolated for reproductive cloning to develop mouse models for biological study, not for medicinal purposes. With the clinical success of adult stem cell therapies, we must ask why some scientists remain fixated on embryonic stem cells. The ability to do reproductive cloning is the only unique aspect of embryonic stem cell research which adult and other stem cells cannot replace. What is the potential return from tax payer funding of embryonic stem cells? No patients have been helped, however, exact genetic clones can now be created [12], mice and monkeys have been created that have two genetic mothers [13] [14], and two fathers can have genetic offspring [15] through the techniques developed from embryonic stem cell research. Adult stem cells are effective and useful for treating patients, embryonic stem cells are needed only for reproductive cloning. It is time for scientists, for the media and for politicians to provide some truthful dissemination of stem cell uses and progress.

REFERENCES

1. Identification of very small embryonic/epiblast-like stem cells (VSELs) circulating in peripheral blood during organ/tissue injuries. Ratajczak MZ, Liu R, Marlicz W, Blogowski W, Starzynska T, Wojakowski W, Zuba-Surma E. 2011, Methods Cell Biol., Vol. 103, pp. 31-54.

2. Marketer, Pharma. South Korean Biotech wins OK for stem cell treatment. Pharma Marketer. [Online] [Cited: Sept 03, 2011.] http://pharma.projectsjunction.com/tag/hearticellgram/.

3. NIH. Clinical Trials. clinicaltrials.gov. [Online] [Cited: Aug 31, 2011.] http://clinicaltrials.gov/ct2/search.

4. Institute, National Cancer. SEER Cancer Statistics Review 1975-2008. Surveillance Epidemiology and End Results. [Online] NIH. [Cited: September 02, 2011.] http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=28&page=sect_28_table.02.html.

5. CDC. Division of heart Disease and Stroke Prevention : Data Trends and Maps. CDC. [Online] [Cited: September 02, 2011.] http://apps.nccd.cdc.gov/NCVDSS_DTM/LocationSummary.aspx?state=United+States.

6. The regenerative medicine laboratory: facilitating stem cell therapy for equine disease. Borjesson DL, Peroni JF. 1, Mar 2011, Clin Lab Med. , Vol. 31, pp. 109-123.

7. Magazine, Time. Stem-Cell Treatments for Pets. Time Magazine. [Online] [Cited: Sept 03, 2011.] http://www.time.com/time/magazine/article/0,9171,1820146,00.html.

8. Pharmacologic immunosuppression. Barshes NR, Goodpastor SE, Goss JA. Jan 1, 2004, Front Biosci. , Vol. 9, pp. 411-420.

9. Regeneration gaps: observations on stem cells and cardiac repair. Murry CE, Reinecke H, Pabon LM. 9, May 2, 2006, J Am Coll Cardiol. , Vol. 47, pp. 1777-1785.

10. Press, Associated. Doctors Question Wisdom, Safety of stem cell treatment Perry had. [Online] [Cited: Sep 03, 2011.] http://www.stemcellpioneers.com/showthread.php?p=14104.

11. Duncan, David Ewing. Health & Medicine : Stem Cell Research. Discover Magazine. [Online] [Cited: Sep 03, 2011.] http://discovermagazine.com/2005/jun/doug-melton-crossing-boundaries.

12. Production of mice using iPS cells and tetraploid complementation. Zhao XY, Lv Z, Li W, Zeng F, Zhou Q. 5, 2010, Nat Protoc., Vol. 5, pp. 963-971.

13. Birth of parthenogenetic mice that can develop to adulthood. Kono T, Obata Y, Wu Q, Niwa K, Ono Y, Yamamoto Y, Park ES, Seo JS, Ogawa H. 6985, Apr 22, 2004, Nature. , Vol. 428, pp. 860-864.

14. Fox, Stuart. DNA Transplantation Yields Monkeys with One Father, Two Mothers. PopSci : The Future Now. [Online] [Cited: Sept 03, 2011.] http://www.popsci.com/scitech/article/2009-08/monkey-born-one-father-two-mothers.
15. Generation of viable male and female mice from two fathers. Deng JM, Satoh K, Wang H, Chang H, Zhang Z, Stewart MD, Cooney AJ, Behringer RR. 3, Mar 2011, Biol Reprod. , Vol. 84, pp. 613-618.

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