Autologous stem cell therapy for Spinal Cord Injury: a regulatory perspective for start-up companies in USA

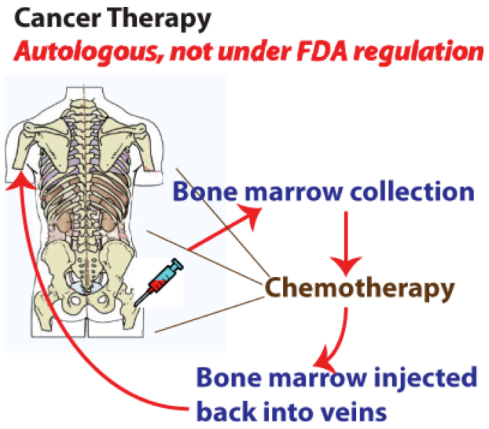
Kamana Misra, PhD, Director Research & Development, Celvive

Spinal Cord Injury (SCI) is a devastating ailment that results in drastic life style alterations for the patients and their immediate family members. For long considered irreversible, impressive research endeavors and advances using stem cell treatments have however ushered in an era of new hope. Today, we stand on the threshold of observing these studies translating into therapies for patients with SCI. A testimonial to the trend is the huge surge in clinical trials attempting to define treatment using stem cells for SCI, majority of them involving "autologous" bone marrow stem cell therapeutics. Unfortunately, not many of these studies have been conducted in US, not due to the lack of research expertise or knowledge, but rather due to general misconceptions in public mind that drive a non-supportive stance of regulatory agencies.

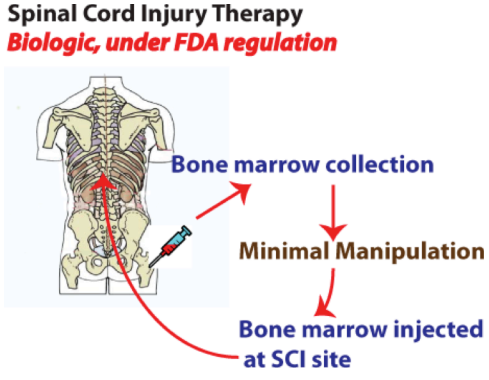
Autologous bone marrow transplant involves collection of stem cells that are normally found in the bone marrow, filtering those cells, and giving them back either to the donor (patient). This type of treatment is exempt from FDA regulation as long as it follows the guidelines for "autologous" use as defined under FDA regulation of human cells tissue and cellular and tissue based products (HCT/Ps) based on following conditions:

- Minimally manipulated
- Autologous use
- Not combined with another article (except water, sterilizing, preservation or storage agents) and
- Either
    - a) Have no systemic or metabolic effect, or
    - b) Be of autologous use, allogeneic use in first or second-degree blood relative.

Is this good news for companies developing therapies using autologous stem cells? Not really. Given the alarming number of clinics that started promoting stem-cell-based interventions without clinical data, the Food and Drug Administration (FDA) had sought an injunction to prevent a US-based company from offering an autologous adult stem cell treatment. In February 2014, D.C. Circuit Court of appeals upheld FDA oversight of autologous stem cell therapeutics. Accordingly it supports FDA stand that cellular therapeutics derived from processes that alter the biological characteristics of cells are no longer "autologous". These are now classified as "Biologics" and require FDA oversight.



A typical example is the treatment of blood malignancies. Cells from peripheral blood or bone marrow are removed from the patient prior to administration of high doses of chemotherapy, stem cells are purified, stored and finally returned to the patient post treatment. This treatment is considered "autologous" and is exempt from FDA approval.



However if you go a step further and use these stem cells for other indications like spinal cord injuries, even in the same patient, the procedure is categorized as a "Biologic" and falls under FDA jurisdiction. Technically an "autologous therapy", it is not classified so by the FDA.

How does this translate for companies developing stem cell therapies for SCI? It indicates a long journey maneuvering through the FDA requirement. It also indicates, for successful navigation, the requirement of significant financial support sufficient to support this path: conditions that prevent many researchers in USA from translating their research into applied cures despite excellent basic research data.

In an attempt to address the challenges faced by US based stem cell researchers, I spoke with Dr. Hatem Sabaawy, MD, PhD, Founder Celvive *Inc*. and the lead investigator of a Phase I/II controlled, single-blind clinical trial for treating early stage, chronic SCI patients with autologous stem cells (clinicaltrials.gov identifier: NCT00816803). His thoughts on the major issues faced by academic research based start-up companies:

Dr. Hatem Sabaawy, M.D., Ph.D.
Assistant professor,
Rutgers, CINJ
Founder of Celvive Inc.

Translational research in an academic environment.
Being part of a thriving research environment offers numerous advantages for staying ahead in cutting edge research. However, commercialization of new treatments is extremely difficult due to monetary limitations and lack of expertise on product development and marketing. Having established the foundation in academia, I had to expedite the developmental process by establishing a start-up company, Celvive Inc.

Funding options for Biotech start-up companies.
Establishing a Biotech company can be a daunting task for a researcher, especially without funding resources. Celvive was established by funding provided by the Foundation Venture Capital Group, a company that provides pre-seed funding to innovative life science companies in New Jersey and helps them advance toward commercialization. Besides funding, the group also provides support for portfolio companies in performing their business transactions, grant management *etc.*, minimizing the companies operating expenses and allowing investment to be utilized for Research & Development. Such pre-seed funding is crucial to sustain a new company through the initial development. Yet, this kind of funding is the most difficult to find. There is a huge demand for funding companies to invest in early development efforts as opposed to most prevalent investment models that look for investing in therapies at later stages of product development.

Stem cell therapy, results from the international clinical trial.
Dr. Sabaawy was the lead investigator for an international study designed to validate promising results obtained from pre-clinical work and animal studies supporting beneficial role for autologous stem cell therapy for SCI patients. The phase I/II clinical trial study was conducted on 70 patients with chronic SCI, previously not responding to treatment for at least 6 months. Using the American Spinal Injury Association Impairment Scale (AIS), patients received neurological and physical evaluations and at the end of 18 months, 23 of the remaining 50 test patients showed a significant improvement of at least 10 points on the AIS motor score with significant sensory and functional improvements, and several

patients were able to walk with assistance. Most importantly, there were no side effects in patients treated with stem cells during the course of our investigation.

Regulatory path in USA.

Since the publication of his study, numerous patients and their physicians have contacted Dr. Sabaawy to explore the possibility of being included in the trial. A safe treatment protocol for improving the quality of life for individuals with SCI has already been established by their international study. Yet, Celvive is not in a position to offer the treatment to patients here in the US until a long-term safety follow up study for patients treated in phase I is completed and the treatment is investigated in a larger number of patients in a phase II dose escalation studies in multicenter trials. The initial response from the FDA has been very encouraging, however, it is extremely important for FDA and other regulatory agencies around the world to look beyond political ramifications and expedite monitored, regulated clinical trials in USA.

Harmonization of clinical trials and treatments for spinal cord injuries.

Despite the tremendous increase in research study numbers in this field all over the world, there is no co-ordination between different study protocols. For example, many investigators use BMSCs for treatment, but there is no standardized protocol for their collection, storage, expansion or injection. This often creates discrepancies in results. There is therefore an urgent requirement to synchronize studies being conducted worldwide. This effort to standardize cell therapies for spinal cord injury was pioneered by Dr. Michael Fehlings, a Toronto-based neurosurgeon, and world expert on spinal cord injury repair and cell therapy. Joining hands with fellow investigators and clinicians from around the globe, they have started a Stem Cell Global Blueprint conference (GBC) to exchange knowledge and define criteria for cell therapies, and to have a unified approach towards the next phase of clinical trials. Besides establishing designs for next set of trials, they also want to ensure better education of the public in context to stem cell therapy.

Conclusion.

Although not a complete cure, adult patient-derived bone marrow cells (ABMCs) can be currently offered as a treatment option for patients with SCI. This study along with numerous other reports shows the beneficial effects of bone marrow derived stem cells. It is clear that the regenerative and secretory properties of bone-marrow derived stem cells can improve symptoms of paralysis in some patients when coupled with the current standard of care that physical therapy provides. However, more studies are needed with a larger number of patients to test different cell dose levels and intervals at which stem cell therapy should be delivered. Since this kind of treatment falls under the “Biologics” preview, there is still a lot to follow up work required to define mechanisms of the beneficial effects. For this work to be followed up successfully in USA, it is extremely important for regulatory agencies to allow regulated follow up studies to be conducted successfully.

Most importantly, public education enabling a systematic patient approach to clinical trial and treatment options including education on accepting therapies offered under protocols approved by local regulatory authorities in co-ordination with international standards is critical. Active participation of public in supporting local regulatory guideline decisions is a sure shot way to ensure un-biased, need-required adoption of regulatory policies