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Commentary

# Regenerative Medicine for Erectile Dysfunction Following Radical Prostatectomy: Are we Ready?

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In an elegantly written paper, Haahr and colleagues from Odense, Denmark, document the first phase 1 trial using autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy. These results have long been awaited. In 2010, Tom Lue's group at UCSF published the first preclinical data on adipose tissue derived stem cell treatment in a rat model of cavernous nerve neuropraxia (a model that accurately and efficiently represents the pathophysiology of erectile dysfunction following nerve-sparing radical prostatectomy) (Albersen et al., 2010). Now six years later, the first clinical trial studying injection of regenerative cells derived from adipose tissue is published in EBioMedicine (Haahr et al., 2016). The advent of the first clinical data forces us as a scientific community to contemplate on whether or not we are ready for clinical translation of stem cell therapy for a non-lethal disease.

## 1. Safety

The trial described is a phase 1 trial, indicating that the primary goal of the project was to evaluate the safety of (in this case) intracavernous injection of autologous unexpanded processed lipo-aspirate, which also has been named adipose stromal vascular fraction (SVF), or as the authors propose, adipose-derived regenerative cells. These cells where harvested using the automated processing Celution® 800/CRS system (Cytori Therapeutics, San Diego, California, USA). Since the harvesting, processing and injection are typically done in one session, it is of capital importance that we gain insight into the contents of the resulting product. The authors clearly showed that the number of injected cells is a direct derivative of the volume of the lipo-aspirate. Furthermore, they show that the age of the patient has no significant influence on the number of cells per gram of adipose tissue in the final processed product. Whether the regenerative capacity of the cellular lysate is impaired with increasing age remains to be elucidated. The composition of the cellular mixture was thoroughly investigated and it was shown that 1.5 (±SD: 0.8)% of the cells where fibroblastoid colony forming units, a subset of which probably represents true mesenchymal stem cells. The authors state that 26% are stromal cells and the markers that are used to define stromal cells in the stromal vascular fraction cells are indeed compliant with the criteria set forth in a position paper by Bourin et al. on behalf of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT) (Bourin et al., 2013). However the true stem cell population within can only be identified by additional criteria including plastic adherence, the ability to differentiate into adipocytes, osteocytes and chondrocytes and a subset of surface markers that is different from those used in the current study. However, the benefits of direct processing possibly outweigh the risks of contamination and possible dedifferentiation of autologous cell cultures. The most important fact is that an overview was given on the contents of the final injected product. The number of cells ranged between 8.4 and 37.2 million cells and is therefore quite variable from patient to patient. The variability in cell number administered would no doubt have direct effects on the clinical outcome. The optimal concentration must be determined in later efficacy studies, and preliminary analyses of the correlation between concentration of cellular lysate, safety, as well as erection recovery were not presented by the authors.

Of capital importance is the fact that no serious adverse events were reported. Adverse events were recorded at each visit by inspection of the injection site and posing the patients an open question, “Did you experience any discomfort related to the operation since the last visit?”, followed by specific questions regarding pain, bleeding and swelling at the liposuction site as well as at the penis area. Five patients reported minor events which can be classified as Clavien Dindo grade I and were mostly related to the liposuction procedure rather than the injection itself. Local penile complaints were limited to one patient reporting penile and scrotal hematoma. No markers of systemic response were assessed in this study thus we cannot determine if systemic changes occurred.

## 2. Efficacy

In the study by Haahr and colleagues, in the incontinent group, 5/6 patients underwent non-nerve sparing prostatectomy while in the continent group, 7/11 patients had some degree of nerve-sparing surgery. Thus, 8/17 patients in total had some degree of nerve sparing surgery,

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and 9/17 patients had non-nerve sparing surgery. If we look at the efficacy data, 9/17 patients were not able to have successful intercourse, and 8/17 patients were able to have successful sexual intercourse. Is this a coincidence? Are the patients with some degree of erection recovery the 8 patients who underwent some degree of nerve sparing surgery? Without additional information about the study cohort we cannot determine if the erection recovery was an effect of regenerative cell injection versus a spontaneous recovery which is to be expected after nerve-sparing surgery (Kaye et al., 2013). One could argue against this position by stating that 4 patients who had an improvement in erectile function where excluded. Early signs of erection recovery however, in our opinion, do not exclude the possibility for later spontaneous improvement of erectile function. The mean time from surgery in the current study was 10.1 months, and it is established that erectile function recovery after nerve sparing radical prostatectomy occurs up to 24 months after surgery (Rabbani et al., 2010).

In the absence of a control group, we simply cannot make any conclusion on the efficacy of the proposed regenerative therapy. A power analysis for efficacy data is lacking, and the incontinent group should not be considered an "internal control" for the following reasons — (1) the rate of nerve sparing surgery in the incontinent group was much lower, (2) authors have described that in their own experience, these patients historically have an impaired erectile recovery and (3) it is well established from centers of excellence that non-nerve sparing results in delayed recovery of continence (Kaye et al., 2013; Gandaglia et al., 2012). As the authors suggested, the efficacy of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy needs to be studied in an adequately powered, randomized and placebo-controlled trial, before any recommendation can be made on the (future) use of this treatment. Even though the wording "potential efficacy" has been used, we believe for the above mentioned reasons that a phase 1 trial is not designed for efficacy evaluation. We have to be rigorous and critical with our conclusions so that others in academic and private centers throughout the world do not prematurely start utilizing this form of local cell-based therapy without appropriately powered studies which show true efficacy. The erectile dysfunction market is large and continues to grow. The risks of financial interests cannot be overestimated and caution is therefore warranted in disseminating and interpreting the reported preliminary efficacy data.

## 3. Ready for translation? Dosage and timing of treatment

The International Society for Stem Cell Research (ISSCR) devised guidelines for clinical translation of stem cell-based therapies which include guidance on the preclinical work up of stem-cell based therapies and the processes involved in clinical translation. Some of the statements pertain to preclinical investigation of mode of action in models that closely resemble the disease state. In young rats, known for their surprising potential for regeneration after injury, we observed only a partial (but significant) recovery of erectile function following cavernous nerve injury (Albersen et al., 2010) after penile injections of high dosages ($1 * 10^6$ cells in animals weighing under 300 g: $\pm 3 * 10^6$ cells/kg) of pure populations of cultured adipose tissue derived stem cells. This clinical trial involves dosages of 8.4 and 37.2 million cells in men with a mean age of 63 years and a mean BMI of 30.3 kg/m$^2$. Assuming, based on their BMI, that these patients weighed at least 80 kg, they received roughly between $1 * 10^5$ and $5 * 10^5$ cells/kg body weight. How does this compare to the situation in a small rodent model? Before we can translate this form of cell-based therapy, concentration response studies, as preliminary reported by Yiou et al. (2015) for bone marrow mononuclear cells, must be conducted. We need to know what minimal concentration of cells could be effective, and what maximal concentration of cells could be safe. The further these two numbers are apart, the better for translational efficacy. In our research we have observed that a critical time-point in cavernous nerve neuropraxia is the first 24 to 48 h after nerve injury, when neuro-inflammation is initiated and influx of neurotoxic subpopulations of macrophages commences (unpublished data and Albersen et al., 2013a). Injected adipose derived stem cells are attracted to the injured neural tissue by the local release of chemokines and cytokines, which is also activated shortly after the initiating events. Several days later, stem cells appear to reside in reticulo-endothelial system sites such as the spleen and bone marrow (Lin et al., 2011). Due to the highly vascular character of the corpus cavernosum, cells disappear rapidly from the penis and definitive evidence of engraftment and differentiation into cell types contained with the corpora has never been established (Albersen et al., 2013b). Although secondary prevention or treatment excludes patients who might recover spontaneously from unnecessary treatment, we hypothesize that early injection, at the time of radical prostatectomy as a primary prevention of erectile dysfunction may be a more valid physiologic-based approach, and potentially more effective, which further spares the patients a separately-timed invasive procedure.

## 4. Future perspectives

We do realize that our comments on the efficacy data in the manuscript by Haahr and colleagues have a negative connotation. This stems from our opinion, and we are convinced the authors share this viewpoint, that any novel therapy offered to our patients should at least undergo rigorously conducted phase 1 and 2 trials before we can consider a novel therapy safe and effective. However, the caution and criticism are intended in a positive and constructive fashion and we applaud the work that the authors have conducted with the intent of providing their patients with a difficult-to-treat sexual dysfunction hope for recovery. There is no doubt that the work conducted by Haahr and colleagues is novel, and extremely important for the advancement of the field of regenerative medicine, and we are eager to witness further progress in the clinical development of their findings.

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