

ORIGINAL ARTICLE

## ALSUntangled Update 3: Investigating stem cell transplants at the Hospital San Jose Tecnologico de Monterrey

### THE ALSUNTANGLED GROUP

#### Overview

At nine months of existence, ALSUntangled (1) has 103 followers on twitter, 50 ALS clinician-scientists from across four countries in our NING, and 22 discussions underway. New discussions since the last update include stem cell transplants in Monterrey Mexico, stem cell transplants at Cell Medicine, and cyclosporine for ALS.

At the request of PALS, we recently reviewed the option of stem cell transplants at the Hospital San Jose Tecnologico de Monterrey. This procedure and its costs (a minimum of \$18,000 plus travel per patient) are detailed on the web (2). Unlike most clinics currently offering stem cell transplants outside of a trial, this group has published its initial experience in a scientific journal (3). Here we analyze this publication, and detail our own patients' experiences with this option.

#### Publication review

There are a number of shortcomings of the manuscript (3). The initial scientific rationale is that CD133+ stem cells obtained from peripheral blood are capable of differentiating into neurons. The authors cite two studies demonstrating the *in vivo* efficacy of CD133+ cells. The first, by Mezey et al., shows that these cells engraft into the brain and express crude markers of neuronal identity – a far cry from what one would expect from a functioning neuron. The second, by Borlongan et al., is in a rat stroke model. The method of neuroprotection is not established and it is unclear that the development of neurons is the etiology for this rescue. It is just as likely that CD133+ cells may provide neuroprotection by a host of other factors (secreted factors, etc.).

There is no clear rationale as to why the authors chose to transplant into the frontal cortex other than to “affect upper motor neuron function”. This seems overly simplistic. There is little discussion about why the specific region along the motor cortex (3–4 cm from the midline) was chosen. It does not appear that a standard ‘cell dosage’ was given. The

ranges reported were from 2.5 to  $7.5 \times 10^5$ . The study is not randomized or blinded. With regard to the baseline demographic data, it is surprising to note that the time from diagnosis to baseline was substantially longer in the treatment group (30.1 months) compared to the control (14.3 months). It is thus likely that these groups were progressing at different rates prior to the study, with the treated group progressing more slowly. Why the authors did not control for this is unclear. The authors also report that upper motor neurons were more affected than lower motor neurons in 50% of the cases but it is unclear how one quantifies what ‘more affected’ means.

In terms of results, the median survival time from diagnosis to end of follow-up was 19 months for control and 66 months for transplanted groups; again, this result may simply be explained by differences in baseline progression rates in the groups, and have nothing to do with how they were treated. Reportedly, the ALSFRS-R score was significantly improved at the six-month time-point following surgery. However, in examining the error bars around these data, it appears that there is tremendous variability in the scores, necessitating further evaluation. Some of the ‘*p*’ values in this analysis are reported as 0.00, which is not scientifically sound.

The authors conclude from their study that “The autologous transplantation of CD133+ stem cells into the frontal motor cortex is a safe and well-tolerated procedure in ALS”. This statement is inaccurate. One patient died 10 days following the procedure from an MI. This means that 1/10 of the subjects died in the first 10 days (10%). Other than survival, the authors document no objective measures of their procedure’s safety or the integrity of the transplants. There were no reported adverse event tables, follow-up MRI scans, measures of upper motor neuron function, or pathological analyses. Were the cells even present at end stage? There were no measures of cognitive function, which could be a concern with bilateral motor cortex injections.

### **Patient experience**

The ALSUntangled investigators are aware of five patients from our clinics who have had stem cell transplants at the Hospital San Jose Tecnologico de Monterrey. While follow-up of these has been limited, to date none of us is aware of any immediate post-surgical complications, or of any objective improvements in them.

### **Conclusions**

We applaud the openness of this clinic in publishing its preliminary results. However, at the present time, there are insufficient safety or efficacy data to support stem cell transplants at the Hospital San Jose Tecnologico de Monterrey as a treatment option for ALS. Also, more rigorous studies are needed to clarify safety and efficacy concerns.

### **The ALSUntangled Group**

The Group currently consists of the following members: Richard Bedlack, Orla Hardiman, Nicholas Marigakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Alberto Ascherio, Bjorn Oskarsson, Alberto

Ascherio, Robert Bowser, Vivian Drory, Jeremy Shefner, Terry Heiman-Patterson, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Lisa Krivickas, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Tahseen Mozaffar, Michael Weiss, John Kissel, Merit Cudkowicz, Jonathan Goldstein, Jeffrey Rothstein, Bryan Traynor, Dan Pastula.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

### **References**

1. Bedlack RS, Hardiman O. ALSUntangled (ALSU): a scientific approach to off-label treatment options for people with ALS using tweets and twitters. *Amyotroph Lateral Scler.* 2009;10:129–30.
2. [www.alsworldwide.org/pdf/stem\\_cell\\_discussion.pdf](http://www.alsworldwide.org/pdf/stem_cell_discussion.pdf)
3. Martinez H, Gonzalez-Garza M, Moreno-Cuevas J, Caro E, Gutierrez-Jimenez E, Segura J. Stem-cell transplants into the frontal motor cortex in amyotrophic lateral sclerosis patients. *Cytotherapy.* 2009;11:26–34.