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## **STEM CELL TRANSPLANTATION INTO THE FRONTAL MOTOR CORTEX IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS TECNOLOGICO DE MONTERREY SCHOOL OF MEDICINE, MONTERREY, MEXICO**

### **INTRODUCTION**

The following is a discussion by Stephen Byer, Co-Executive Director, [stephenbyer@alsworldwide.org](mailto:stephenbyer@alsworldwide.org) and Michael E. Schafer, M.D., Medical Director, [meschafer@alsworldwide.org](mailto:meschafer@alsworldwide.org) of ALS WORLDWIDE, provided for the benefit of ALS patients and their families. ALS WORLDWIDE is a non-profit organization that provides support to ALS families internationally through scientific research interpretation, individual patient advocacy and community activism.

### **BACKGROUND INFORMATION OF THE STEM CELL TRANSPLANTATION FOR ALS PATIENTS**

The initial clinical test study result of the stem cell procedure referred to above, instituted by Tecnologico de Monterrey School of Medicine, was published in *Cytotherapy*, February, 2009. It is considered by many within the international neurological community to be the foremost procedure available today for minimizing or abrogating the symptoms of ALS and extending the lifespan for those with the disease. It is a state of the art use of autologous CD-133 (+) stem cells injected into the frontal cortices for the effective stimulation and reinnervation of existing motor neurons and possible formation of new motor neurons. Clinical test studies were conducted over a two-year period during which results were confirmed through both clinical observation and MRI tractography. Dr Michael Schafer and Stephen Byer first identified the procedure in 2007, have since jointly pursued its use for the ALS community worldwide and visited Tecnologico de Monterrey School of Medicine in March, 2009. Barbara and Stephen Byer, representing ALS WORLDWIDE and the patient community they serve, were in Monterrey in June, 2009 and in August 2009, to observe the hospitalization and procedures for the several international research subjects who were provided this stem cell therapy.

### **PRIMARY PHYSICIAN CO-AUTHORS OF THE CLINICAL TEST STUDY**

Dr. Hector Ramon Martinez--Principal Investigator for the ALS Stem Cell Transplant Program; Neurology Professor appointed as Chairman for the Neurodegenerative Disease Research Chair at Tec de Monterrey School of Medicine.

Dr. Enrique Caro--Chief of Neurosurgery; Hospital San Jose Tecnologico de Monterrey, Sub-investigator and Professor of Neurosurgery, Tec de Monterrey School of Medicine.

Dr. Maria T. Gonzalez-Garza--Researcher, Professor of Stem Cell Therapy Chair; Tec de Monterrey School of Medicine

Dr. Jorge E. Moreno-Cuevas---Coordinator Stem Cell Therapy Chair; Tec de Monterrey School of Medicine

Dr. Jose J. Segura---Neurology Service, University Hospital

### **DESCRIPTION OF PROCEDURE**

The procedure involves the withdrawal of peripheral blood\*\* from ALS patients to procure and refine CD133(+) stem cells, injecting cells into the frontal motor cortex of the brain toward the purpose of delaying further progression of ALS, extending life and improving the quality of life. The procedure is performed by a neurological surgical team led by Dr Enrique Caro, Chief of Neurosurgery and Professor of Neurosurgery at Hospital San Jose Tecnologico de Monterrey.

\*\*Peripheral blood stem cells (PBSC's) are one source of cells for hematopoietic (blood-forming) cell transplant recipients. PBSCs circulate in the bloodstream, and are collected from the patient using a process called aphaeresis. Whole blood passes through a large bore blood catheter from the patient into a machine that separates out nucleated cells (stem cells have nuclei) and returns the remaining blood components back to the patient. In the three days immediately prior to the procedure, patients receive an injectable marrow stimulate called G-CSF (Neupogen) to increase the numbers of stem cells in the blood. Once collected, the PBSC are then injected into the frontal motor cortex of the patient or frozen for use later.

## **SAFETY OF PROCEDURE**

After 39 procedures performed since 2005, there has been no incidence of significant adverse events during or following surgery. The procedure is minimally invasive, performed under local anesthesia and intravenous sedative, and takes approximately 90 minutes. Operating rooms, equipment, technology and surgical procedures are all of the highest international standards. Those approved for the procedure are considered research subjects and their hospitalization, surgical procedure and treatment, both before, during and after discharge, are all within the same highest standards as those who participated in the original Phase I and II of the clinical test study.

## **THE JUSTIFICATION FOR USAGE OF CD133 (+) STEM CELLS**

In the words of Dr Jorge Moreno-Cuevas, MD, PhD and Coordinator, Stem Cell Therapy Chair, Tec de Monterrey, "CD133 (+) stem cells are trans-differentiated--they express genes that correspond to motor neurons even before the addition of differentiators or being in contact with existing motor neurons." Through the stimulus of Neupogen, a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology, the CD133 (+) cells achieve great plasticity, or stem cell differentiation. Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

## **DURATION OF HOSPITALIZATION**

Research subjects are advised to arrive in Monterrey on the Sunday prior to their scheduled procedure. They will check into a local hotel for the first 3 nights. Monday morning, they are to be at the hospital at 8 AM for a meeting with the Stem Cell Research and clinical team, the review and signing of an Informed Consent letter, their first Neupogen injection and to have an MRI, returning to their hotel for the night. Tuesday and Wednesday mornings, they again need to report to the hospital for their second and third Neupogen injections. Wednesday noon, the research subject must report to the hospital for the catheter and spend that night in the hospital. Thursday morning, the aphaeresis is performed. Thursday afternoon, the CD133(+) stem cells are injected into the frontal motor cortices of the research subject. Friday morning the research subject is released and returns to the hotel for a recommended two more nights, returning home on Sunday. Both before and after hospitalization stays, the research subject is free to enjoy the many wonderful sights Monterrey has to offer.

## **FUNDING OF RESEARCH**

Tecnologico de Monterrey is committed to finding new treatment opportunities for ALS patients and the development of world class scientific advancement for this devastating disease. To meet these objectives, a major fundraising campaign is currently underway to provide support for ongoing and expansive research efforts to develop new and more effective protocols and facilitate enrollment of additional subjects. Providing total care for the Adult Stem Cell Transplantation Protocol is currently estimated to be \$46,000 for each research subject.

Funding for this research protocol is dependent upon donations from individuals, corporations and foundations who support efforts to assist the ALS community of patients. While no one is required to provide a donation, those who wish to participate in the protocol are urged to contribute funds for their standard care, which includes hospitalization, nursing and physician care and any tests required. This part of the cost per patient is \$18,000 USD. Research subjects are also responsible for all travel expenses and any additional hospital charges or other clinical situation that may arise unrelated to the protocol.

The balance of funds required for the research aspect of the protocol rely upon the limited current resources from the Zambrano Hellion Fund and the Stem Cell Research Chair, as well as individual and corporate grants. Approximately \$28,000 reflects the individual cost per research subject. Therefore, donations to the research aspect of this protocol are greatly appreciated. Support of Tecnologico de Monterrey, to whatever extent is possible, benefits the ALS community throughout the world.

## **TRAVEL**

ALS WORLDWIDE, together with Tec de Monterrey, assists in the planning and scheduling of travel needs, including transfer to and from the airport, hotel, incidental expenses and any other needs an ALS patient family may have. Hotel accommodations in Monterrey are available at the Quinta Real, a beautiful, comfortable and most accommodating 6-star establishment at which a reduced rate is provided patients traveling to Monterrey for the Stem Cell Procedure. Any questions, concerns or requests can be addressed via email or telephone. Once the research subject arrives in Monterrey, both medical and administrative contact personnel are provided who can assist and advise you with answers to any questions.

## **STANDARD TESTS PERFORMED**

The standard tests will likely include all of the following: General physical examination, review of ALS symptoms and progression, cardiological evaluation, spirometry test, complete blood evaluation including coagulation profile, respiratory analysis and cranial MRI tractography (visual reconstruction of neural connections). Multiple tests will be performed as needed when determined by attending physicians.

## **ANTICIPATED RESULTS FROM PROCEDURE**

"This stem cell procedure is not a cure. We offer nothing more than the expectation of stability and probable extended life expectancy. The opportunity, however, exists for improvement through reduced symptoms." These words, stated by Dr Hector Ramon Martinez, Principal Investigator of the stem cell program, should serve as the overriding, and operative, viewpoint and should set the level of expectation for prospective research subjects and their families.

## **DESCRIPTION AND STANDARDS OF HOSPITAL**

Hospital San Jose Tec de Monterrey is a world-class hospital accredited by the Joint Commission International for its high quality and best-in-class patient care. Since 1969, it has focused on the well-being of its patients by providing innovative technology, highest standards of care, experienced and notable medical professionals and diligent procedures. The International Patient Office provides highest quality personalized services and ensures a comfortable stay for all patients and their families. Hospital San Jose provides all clinical, emergency care, organ transplant, laboratory, radiological, dialysis, medical evaluation and diagnostic services. Its standards of excellence and proficiency allow it to be ranked among the world's most respected medical institutions.

## **MEASUREMENT OF PRE- AND POST-PROCEDURE RESULTS**

Detailed physical examination, use of ALSFRS (ALS Functional Rating Scale) and cranial MRI (magnetic resonance imaging) tractography are all performed at initial hospitalization and again at six months and 12 months post-procedure at Hospital San Jose (for which the primary expense incurred is airfare). In this manner, ALSFRS and physical examination data is accrued and then compared to, and hopefully supported by, tractography imaging that will show differences in neuronal axon connections. Other research subject follow-up examination costs incurred at Tecnológico de Monterrey, usually quite minimal, are borne partially by Tecnológico de Monterrey and partially by research subjects. Subjects are advised to also secure physical examinations from their local physicians periodically during the first year post-procedure.

## **FURTHER STEM CELL PROCEDURE(S)**

A plan now exists, to be confirmed by the completion and acceptance of a formal protocol, to provide a follow-up stem cell injection one year after the original procedure. This is based on the obvious understanding that neuronal replenishment initially provided through the procedure is partially offset by the programmed cell death (apoptosis) that is the unfortunate hallmark of ALS. A gain of some neuronal activity affording increased mobility and decreased symptoms will eventually be "overwhelmed" by the loss of other neurons. This reinforces our grasp that the stem cell protocol must be viewed as a treatment and not a cure. It is expected that second and thereafter procedures will be available at a substantially lowered cost and resultant donation by the research subjects and will require a shorter duration at Hospital San Jose than the original stay. Careful study of the research subject population thus far clearly suggests that the second procedure should be conducted at a 12-month interval following the first procedure.

## **MAJOR PROTOCOL MODIFICATIONS FOLLOWING PHASE I AND II CLINICAL TEST STUDIES**

The initial Phase I and II clinical test studies were accomplished using a substantially smaller number of autologous CD-133 (+) stem cells than are now being injected. Whereas the initial number of cells was approximately 250,000 for each of two injections into the frontal cortices, this has been systematically increased to a general range of 5,000,000-7,000,000 for each injection. This provides a better result and a longer time frame prior to the need for a second procedure while maintaining the impeccable safety record demonstrated thus far. The number of injected stem cells is patient-specific and determined by gender, age, body mass, cell availability and other factors considered by the research team.

## **THE CITY AND TECNOLÓGICO DE MONTERREY**

Monterrey is a safe and beautiful city, the third largest in Mexico, and considered the cultural capitol of the country. It is surrounded by beautiful mountain ranges and is easily accessible by air into its international airport, code MTY. Hospital San Jose is part of the largest educational, health service and biotech organization in Mexico—ITESM (Monterrey Institute of Technology and Higher Education), commonly shortened to Monterrey Institute of Technology (*Tecnológico de Monterrey*). Tecnológico de Monterrey is a Mexican private educational

institution that was founded in 1943. Its campuses are distributed throughout the country and academic centers are in Mexico and other Latin American countries; it also has international offices in North America, Europe, and Asia. Through its Virtual University it is present all over the world, by means of learning networks and advanced information technologies. Based in Monterrey, the Institute has 34 campuses in 25 cities throughout the country and is known for becoming the first university ever connected to the Internet in Latin America and the Spanish-speaking world, having one of the top graduate business schools in the region and being one of the leaders in patent applications among Mexican universities.

### **RESEARCH SUBJECT SCHEDULING**

Prospective research subjects, their families and physician(s) should consult together to determine whether or not this is something you wish to pursue. If so, ALS WORLDWIDE will then be happy to coordinate obtaining and sending your medical records to Tecnológico de Monterrey and assist in the scheduling of your medical visit. Tec de Monterrey may need to obtain information from the physician now in charge of the patient for additional data and to be in contact during follow-up. Tec de Monterrey will require a prior summary of clinical data as well as neurophysiologic studies and existing cervical and cranial Magnetic Resonance Imaging. After admission to the protocol, the research subject will submit to an MRI tractography (reconstruction of neural connections) at Hospital San Jose.

Alternatively, research subjects may choose to do the scheduling themselves. There is no charge or fee, directly or indirectly, from ALS WORLDWIDE in providing these services. It is the fulfillment of our stated goal to support ALS patients and families internationally through scientific research interpretation, individual patient advocacy and community activism. Those who wish to handle all scheduling activities directly should advise ALS WORLDWIDE by email and all contact information for the appropriate individuals at Tec de Monterrey will be provided.

### **ADDITIONAL INFORMATION**

Here are several links to interesting and worthwhile information relating to the procedure and organizations described in this document. We urge that all prospective applicants carefully review each of them prior to any decision as to the advisability of this protocol.

[Cytherapy, February, 2009 Clinical Test Study Phase I](#)

[Motor Cortex in Brain Function](#)

[Scientific Abstracts of Monterrey Stem Cell Procedure and Related Studies](#)

[Scientific Data about CD133 Stem Cells](#)

[Information about Tecnológico de Monterrey \(ITESM\)](#)

[Hospital San Jose Tec de Monterrey](#)