



#### AUTHORS

Chaim Lebovits  
 Ralph Kern, M.D., MHSc  
 Yael Gothelf, Ph.D.  
 Yossef S. Levy, Ph.D.  
 Revital Aricha, Ph.D

BrainStorm Cell Therapeutics Ltd.,  
 12 Bazel Street,  
 POB 10019 Petach Tikva, Israel.

## NurOwn®: BrainStorm's innovative stem cell therapy for ALS and neurodegenerative diseases

**B**rainStorm Cell Therapeutics has developed NurOwn®, a proprietary technology based on bone-marrow-derived mesenchymal stem cells (MSCs) that are induced in culture to produce and deliver neurotrophic factors (NTFs). We are developing this innovative technology for the treatment of various neurodegenerative diseases with the goal of helping neurons repair or recover. NurOwn® has been tested in several animal models of neurodegenerative diseases and has shown safety and promising signs of efficacy in mid-stage clinical trials for participants with amyotrophic lateral sclerosis (ALS).

### Neurodegenerative diseases and stem cell research

Neurodegenerative diseases such as ALS, Parkinson's disease, Huntington's disease, Alzheimer's disease, multiple sclerosis and autism affect millions of people around the globe, and for the most part lack effective therapies. The need for therapies that can replace or repair dying or damaged neurons has led investigators to develop and evaluate stem-cell-based therapies as an innovative regenerative medicine treatment modality in neurodegenerative disease<sup>1-4</sup>.

In general, there are two distinct, and potentially complementary, approaches to treating neurodegenerative diseases with cellular therapies. Stem cells may be used either to replace or to support and protect dying or damaged neurons through a variety of mechanisms, including quieting the immune system to reduce neuroinflammation, and secretion and delivery of NTFs to support neuronal repair.

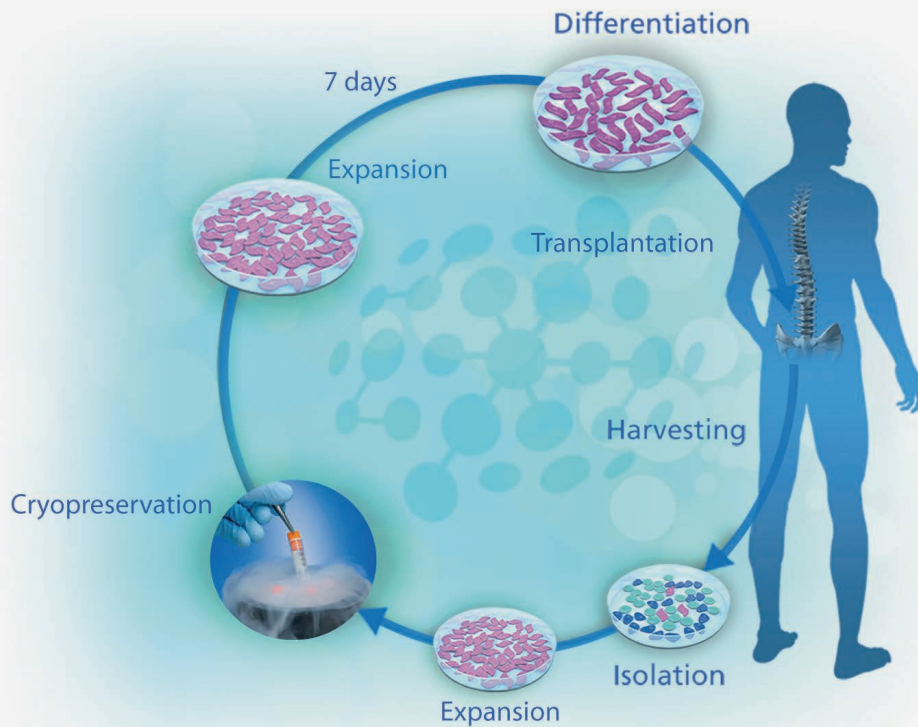
The replacement approach presents several important technical challenges, particularly in neurology — one must not only deliver neurons, or cells that will turn into neurons, but also ensure that the neurons delivered are in the right place and make the right connections, with other neurons in the central and/or peripheral nervous system or with target tissues such as muscles. Mesenchymal stem cells (MSCs), are an example of the protective approach and have been used to treat a variety of conditions, including neurodegenerative diseases.

NurOwn® is a technology platform that builds on the enormous research efforts that have gone into developing MSCs as a treatment for a variety of human diseases. BrainStorm has taken MSCs a step further in developing NurOwn® as a differentiated, autologous, MSC therapy customized for the treatment of several neurodegenerative diseases (see **Fig. 1**).

### Mesenchymal stem cells

MSCs are multipotent precursor cells found in many tissues, but they are most commonly harvested from bone marrow, adipocyte tissue or placenta. MSCs have been used in human studies since the 1990s, initially to enhance engraftment of bone-marrow transplants. Eventually researchers discovered that MSCs are able to dampen the immune system in a variety of beneficial ways<sup>5,6</sup>.

This led to studies of MSCs for the treatment of various immunological and inflammatory disorders — such as graft-versus-host disease, inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis — as well as



**Figure 1 | Generation of NurOwn®.** Bone marrow is removed from the patient, and MSCs are isolated in culture and cryopreserved. Before each treatment, MSCs are thawed and induced to separate into MSC-NTF cells, which are then transplanted back to the patient.

cardiovascular disease, stroke, kidney disease, and many other areas. Hundreds of clinical trials have been completed or are ongoing for MSCs in various conditions.

### How NurOwn® makes an improved MSC

Where others have ended with MSCs is where BrainStorm begins. Our patented NurOwn® technology grows MSCs in proprietary conditions to convert them into differentiated biological factories capable of secreting a variety of NTFs, which support the survival of neurons in a variety of conditions and are beneficial in animal models of many neurodegenerative diseases.

The NurOwn® core technology was invented in the laboratories of Professors Daniel Offen and the late Eldad Melamed at Tel Aviv University in Israel, and has been developed and advanced by Brainstorm for more than a decade.

NurOwn® NTF-secreting MSCs (MSC-NTF cells) are designed to treat neurodegenerative diseases by enabling the delivery of several NTFs at or close to the site of neuronal injury. MSC-NTF cells also possess immunomodulatory characteristics common to their MSC of origin, and in

some neurodegenerative disorders, this may address an important mechanism of disease modification. MSC-NTF cells secrete a variety of NTFs, including glial-derived NTF (GDNF), brain-derived NTF (BDNF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF). We have found MSC-NTF cells to be effective in animal models of ALS, Parkinson's disease, multiple sclerosis<sup>7</sup>, optic nerve transection<sup>8</sup>, and Huntington's disease.

More than 60 patients with ALS have been treated with MSC-NTF cells in early<sup>9</sup> and mid-stage<sup>10</sup> clinical trials conducted in the United States and Israel, which have established its strong safety and tolerability profile and shown promising signs of efficacy.

BrainStorm hopes to develop a disease-modifying therapy with the potential to halt or reverse ALS progression.

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