NsGene is a Denmark and US-based biotechnology company located in the Copenhagen area and in Providence, RI. Established in 2000 in Denmark, the company established its US operation in 2011. The Company has developed an innovative, implantable, Brain Repair platform to treat neurological disorders with great unmet medical needs and has a strong focus on Parkinson’s disease (PD). Dr. Wahlberg is a board certified neurosurgeon, researcher, and founder and is joined by a team of scientists with experience and expertise in neuroscience and biotechnology product development. The company has successfully brought its technology from R&D into clinical studies and has gathered the necessary internal and external resources and facilities to support its R&D efforts, GMP production, regulatory submissions, and clinical trials. The company has R&D facilities both in Denmark and Providence and employs 10 people.

Opportunity Overview

The Brain Repair product is a brain implantable device, comparable in diameter to a deep-brain stimulating electrode used in the treatment of PD. However, instead of electricity, the device delivers potent therapeutic proteins to the degenerating dopaminergic neurons and nerve endings in the brain (striatum) to confer both neuroprotective and regenerative therapeutic effects. The treatment is, therefore, not only aimed at symptoms but also seeks to modify the course of the disease by repairing dopaminergic neuron function and halting progressive cell degeneration.

The Brain Repair product for the treatment of PD consists of a slender tubular device with an approximately 2 cm long hollow fiber compartment at its tip containing a genetically engineered human cell line secreting glial cell line-derived neurotrophic factor (GDNF). The hollow-fiber membrane allows for the influx of nutrients and the outflow of the therapeutic factor(s) but prevents direct contact of the cell line and the host brain. These bioreactor-like devices can be introduced bilaterally into the putamen of the brain using standard stereotactic neurosurgical methods currently available in essentially all major neurosurgical centers. Multiple devices (3 on each side) can be combined to achieve therapeutic levels in the entire putamen, thereby overcoming the obstacles of competitive technologies such as in vivo gene therapy and pump and catheter technologies. Devices provide for long-term factor secretion of de novo synthesized protein while allowing for their retrieval or replacement, thus alleviating the safety and regulatory concerns associated with direct cell or gene based therapies. In addition, the permselective membrane confers immune protection of the allogeneic cell line, allowing the use of the same parental cell line bank to produce various therapeutic cell lines in multiple products and individuals. In combination with a shared clinical interface, this allows for a commercially attractive product platform as all Brain Repair therapy products share manufacturing, regulatory frameworks, and end-users. Beyond GDNF, the product platform is capable of delivering any cell-derived substance to the CNS providing a controlled, site-specific, and safe delivery of a variety of therapeutic substances or combinations thereof. To achieve high factor secretion levels, NsGene has developed proprietary expression technologies allowing its human cell line to stably produce large quantities of GDNF or other gene products. The long-term stability (>1 year) of this deliver been demonstrated in animal models and clinical trials. For chronic treatments,
every 2-5 years, an implantation system is under testing that allows for relatively easy retrieval and replacement (if needed or desired) without the need for new imaging or stereotactic neurosurgical instrumentation.

This product platform represents an investment/partnering opportunity into a pipeline of products for the treatment of PD and other severe neurological disorders.

**Details of MJFF Grant**

This project builds on a MJFF LEAPS grant entitled “Encapsulated GDNF-Producing Cells for Neuroprotection in Parkinson’s Disease”. The milestone-based funding has been used to support the long-term safety and performance of experimental devices secreting GDNF in normal and Parkinsonian rats and clinical devices in a GLP compliant study in normal Goettingen minipigs to support an IND application and transition into clinical development.

**Results and Potential Next Steps**

Clonal GDNF secreting cell lines generated from a bank of the human retinal pigment epithelial cell line used for the platform technology and tested for expression and function *in vivo*. A high expressing and stable clone was selected as a clinical candidate cell and further tested *in vitro* and *in vivo* in experimental and clinical devices. Experimental GDNF-secreting devices showed long-term function in the rat striatum for at least 14 months and conferred both strong neuroprotective and neurorestorative effects in 6-OHDA lesioned animals. The selected GDNF-secreting cell line was banked under GMP and used in a subsequent IND enabling safety study. A clinically applicable polysulfone hollow fiber membrane was manufactured in house and used to make clinical device prototypes. An internal scaffolding to support cell adhesion and viability was optimized. A large animal Goettingen minipig model enabling MRI guided stereotactic implantation of the putamen was set up and pilot studies of clinical prototype devices were tested for 1 and 3 months. The final device configuration was tested in a 6-month IND enabling study under GLP compliance. This study showed that two devices bilaterally (4 per animal) can be implanted and retrieved safely while providing long-term therapeutic levels of GDNF throughout the putamen that upregulate the appropriate dopaminergic machinery. Histopathological analyses confirmed the safety of this approach as minimal tissue reaction to the implants was observed. In conjunction with other documentation, these data will be used to file an IND in the first half of 2015 to support a planned Phase Ib trial in approximately 12 patients with PD. This trial will demonstrate safety and feasibility as primary outcomes but is also designed to yield important PET and clinical outcome data to support investments in further clinical development. We are seeking an early partner to support the transition to clinical development and commercialization.

**Intellectual Property Status**

NsGene owns strong and broad IPR covering its Brain Repair platform. Several patent families protect the Brain Repair platform. In addition, NsGene has made strategic licensing deals to secure freedom to operate in its product development. Third party royalties on in licensed technologies are...