Targeted delivery of nerve growth factor via encapsulated cell biodelivery in Alzheimer disease: a technology platform for restorative neurosurgery

Clinical article

LARS U. WAHLBERG, M.D., PH.D., 2,5 GÖRAN LIND, M.D., 1 PER M. ALMQVIST, M.D., PH.D., 1,5 PHILIP KUSK, PH.D., 5 JENS TORNØE, PH.D., 5 BENGT JULIUSSON, PH.D., 5 MICHAEL SÖDERMAN, M.D., PH.D., 3 EVA SELLDÉN, M.D., PH.D., 4 ÅKE SEIGER, M.D., PH.D., 2 MARIA ERIKSDOTTER-JÖNHAGEN, M.D., PH.D., 2 AND BENGT LINDEROTH, M.D., PH.D. 1

Departments of 1Neurosurgery, 2Geriatric Medicine, 3Neuroradiology, and 4Anesthesiology, Karolinska University Hospital, Stockholm, Sweden; and 5NsGene A/S, Ballerup, Denmark

Object. The authors describe the first clinical trial with encapsulated cell biodelivery (ECB) implants that deliver nerve growth factor (NGF) to the cholinergic basal forebrain with the intention of halting the degeneration of cholinergic neurons and the associated cognitive decline in patients with Alzheimer disease (AD). The NsG0202 implant (NsGene A/S) consists of an NGF-producing, genetically engineered human cell line encapsulated behind a semipermeable hollow fiber membrane that allows the influx of nutrients and the efflux of NGF. The centimeter-long capsule is attached to an inert polymer tether that is used to guide the capsule to the target via stereotactic techniques and is anchored to the skull at the bur hole.

Methods. Six patients with mild to moderate AD were included in this Phase Ib open-label safety study and were divided into 2 dose cohorts. The first cohort of 3 patients received single implants targeting the basal nucleus of Meynert (Ch4 region) bilaterally (2 implants per patient), and after a safety evaluation, a second cohort of 3 patients received bilateral implants (a total of 4 implants per patient) targeting both the Ch4 region and the vertical limb of the diagonal band of Broca (Ch2 region). Stereotactic implantation of the devices was successfully accomplished in all patients. Despite extensive brain atrophy, all targets could be reached without traversing sulci, the insula, or lateral ventricles.

Results. Postoperative CT scans allowed visualization of the barium-impregnated tethers, and fusion of the scans with stereotactic MR images scan was used to verify the intended positions of the implants. Follow-up MRI at 3 and 12 months postimplantation showed no evidence of inflammation or device displacement. At 12 months, implants were successfully retrieved, and low but persistent NGF secretion was detected in half of the patients.

Conclusions. With refinement, the ECB technology is positioned to become an important therapeutic platform in restorative neurosurgery and, in combination with other therapeutic factors, may be relevant for the treatment of a variety of neurological disorders. Clinical trial registration no.: NCT01163825. (http://thejns.org/doi/abs/10.3171/2012.2.JNS11714)

Key Words • encapsulated cell • nerve growth factor • Alzheimer disease • clinical trial • restorative neurosurgery • functional neurosurgery • stereotaxy • cholinergic forebrain

Targeted administration of regenerative proteins, neuromodulatory peptides, neurotransmitters, and therapeutic antibodies in relevant anatomical areas carries great potential for the treatment and modification of many neurological disorders, including neurodegenerative disorders and epilepsy. Several techniques have been developed for the delivery of therapeutic compounds to the CNS, including intrathecal or intracerebroventricular drug delivery via infusion pump systems, convection-enhanced delivery, 4 and gene therapy. 5 Convection-enhanced delivery is the continuous positive pressure injection of a fluid containing a therapeutic agent into the parenchyma, in which convection is the driving force in delivering the drug over the required distances. Convection-enhanced delivery can distribute small-molecule drugs as well as protein therapeutics, and high drug doses combined with convection can be advantageous in situations in which a larger brain structure must be treated. Pump systems allow one to cease or modulate the dose of the therapeutic substance; however, all pump systems require expensive hardware and refilling. This technology

Abbreviations used in this paper: AD = Alzheimer disease; ECB = encapsulated cell biodelivery; NGF = nerve growth factor.
also becomes cumbersome when delicate or multiple discrete regions need to be treated. Furthermore, the stability and potency of the drug in the pump reservoir may vary and decline over time, and antigenicity to an inadequately formulated protein may develop as well.

Viral vector–mediated gene transfer can express a therapeutic gene and deliver regional doses of potent biologics long-term without the need for refilling or replacement. However, once delivered to the patient, current gene therapy cannot be terminated, nor can a delivered dose be modified or properly assessed. Permanent genetic modification of a patient’s brain cells raises several safety and regulatory concerns requiring tedious development and long-term follow-up of patients beyond the completion of clinical studies.

Encapsulated cell biodelivery is a technology platform that aims to combine the potency of gene therapy with the safety of an enclosing and retrievable device (Fig. 1). The technology targets diseased neurons with therapeutic biological substances continuously produced and secreted by a genetically engineered human cell line enclosed within a retrievable implant. The cell line is protected from immune rejection by the semipermeable membrane, and thus no immunosuppression is required. The technology is capable of making practically any cell-derived therapeutic, including recombinant growth factors, peptides, and antibodies. In the current study, the ECB technology was designed to secrete human NGF and was applied to the diseased cholinergic cell populations in the basal forebrain of patients with AD.

Common to all patients with AD is the degeneration of the central cholinergic system. It has been hypothesized that basal forebrain cholinergic neurons and cortical and hippocampal projection neurons degenerate in AD because of the loss of neurotrophic support from their target sites, which produce endogenous NGF. This protein has well-known neurotrophic effects on basal forebrain cholinergic neurons in animals and prevents cholinergic neuron degeneration caused by injury, excitotoxicity, aging, or amyloid overexpression. The endogenous NGF signal is normally retrogradely transported from the production areas in the cortex and hippocampus to the cholinergic nuclei in the basal forebrain. The mechanisms behind the reduced neurotrophic support in AD are not completely understood, but deficits in this transport and/or signaling of NGF may be pivotal.

Positive effects of NGF on cell survival and neurological functionality have been demonstrated in several animal studies, which indicate that sustained local delivery of NGF to the cholinergic basal forebrain can arrest and even reverse the degeneration of the basal forebrain cholinergic neurons involved in the cognitive decline in AD. Clinical data from NGF infusion and gene therapy studies have supported these findings in animals.

Given these functional and nonclinical safety data on the ECB technology, we set out to explore the safety, tolerability, and biological effects of ECB of NGF in patients with mild to moderate AD. Here, we describe the first clinical trial of the implantation and retrieval of ECB implants secreting human NGF bilaterally placed in the basal forebrain of 6 patients with AD. We discuss device- and procedure-related aspects and considerations regarding this novel technology. Note that information on the study design, objectives, and outcome measures regarding the technology’s safety, tolerability, and efficacy are presented in more detail elsewhere.

### Methods

This clinical trial, no. NCT01163825, is registered with the ClinicalTrials.gov database (http://clinicaltrials.gov). The Swedish Medical Products Agency and the regional human ethics committee of Stockholm approved the study protocol. Both patient and caregiver gave oral and written informed consent prior to study entry.

**Establishing the NGF-Expressing NGC-0295 Cell Line**

Human NGF cDNA was amplified from HEK293 genomic DNA via polymerase chain reaction. The am-
plified fragment was cloned in pcDNA3.1(+) (Invitrogen). Subsequently, the cytomegalovirus promoter was replaced with the cytomegalovirus promoter/chimeric intron from pCI-neo (Promega). The resulting vector was named pCI\_hNGF.

ARPE-19, a spontaneously immortal human retinal pigment epithelial cell line (American Type Culture Collection), was grown at 37°C in 5% CO₂. Growth medium consisted of DMEM/Nutrient Mixture F-12 with GlutaMAX (Invitrogen) supplemented with 10% fetal bovine serum (HyClone). Native cells were transfected with pCI\_hNGF using Fugene (Roche) according to the manufacturer’s instructions. Clones were selected using G418 (Sigma-Aldrich), and single colonies were isolated and expanded. Clones producing high levels of NGF were further characterized with regard to long-term NGF expression and stability in conventional cell culture and in NsG0202 devices. Encapsulation studies were performed both in vitro and in vivo.

NGC-0295 was selected from an initial set consisting of more than 200 isolated clones, and the in vitro expression level was approximately 300 ng/10⁶ cells/24 hrs.

The amount of NGF released by each capsule was sampled in 1 ml of human endothelial serum-free medium (Invitrogen) over a 4-hour incubation period. Nerve growth factor concentrations were measured using a sandwich enzyme-linked immunosorbent assay (R&D Systems). Standards and samples were assayed in duplicate according to the manufacturer’s instructions. Results were expressed in nanograms of NGF per 24 hours after extrapolation.

**Producing the Clinical Device NsG0202**

The NsG0202 device was produced under good manufacturing practices (Fig. 1). In a cleanroom facility (NsGene A/S), a 150-mm-long, 1-mm-wide, hollow, barium-impregnated polyurethane tether (Carbothane, Lubrizol Corp.) was attached to an 11-mm-long polyether-sulphone hollow fiber membrane (Akzo, Membrana) via a titanium linker (Heraeus Materials, S.A.). The hollow fiber membrane has an outer diameter of 0.72 mm and a mean molecular weight cutoff of 280 kD. The tether-linker-membrane junction was secured with ultraviolet-cured acrylic-based glue (Dymax Corp.), and the membrane void was fitted with a cored polyvinyl alcohol cylindrical foam matrix (Clinicel, M-PACT). Devices were subjected to a quality control process, packaged, and sterilized with gamma radiation (Isotron). The NGC-0295 cells, produced in a cell bank under good manufacturing practices, were cultured as described above, and the hollow fiber was filled with the NGC-0295 cells. Aseptic filling of the device and storage of the NsG0202 devices were performed using custom equipment and packaging (Vecura). Filled devices were kept in sealed sterile containers filled with human endothelial serum-free medium at 37°C for 4.5 weeks and were tested for sterility, mycoplasma, cell leakage, and NGF production before being released. A shelf life of 5 weeks after release was validated for the study. On the day of surgery, devices selected for implantation were transported to the neurosurgical department in a tamper-proof box thermally insulated with warm packs and were stored in the operating room until use.

**Clinical Study Design**

The study was designed as a 12-month, open label, single center, Phase Ib, dose-escalation study of the ECB of NGF to the cholinergic basal forebrain of patients with mild to moderate AD. Six patients were enrolled. Prior to enrollment, patients had undergone medical examination at a memory clinic, including a medical history from a close informant, and assessment of somatic, neurological, and psychiatric status, as well as CT or MRI studies. Study inclusion criteria consisted of the following: a diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria, a patient age of 50–80 years, a Mini-Mental State Examination score between 15 and 24, life at home with a caregiver, and treatment with a stable dose of acetylcholinesterase inhibitors. Exclusion criteria included concurrent medical and/or psychiatric conditions treated with antipsychotic drugs.

**Surgical Implantation**

Anesthesia and Perioperative Imaging. Patients were admitted to the neurosurgical ward the day before surgery for physical examination and routine blood analyses. On the day of surgery general anesthesia was induced with intravenous propofol infusion (2 mg/kg) and a bolus of fentanyl (50–100 μg) before attaching the stereotactic frame. The Leksell stereotactic frame (Model G, Elekta) was attached with the anterior pins placed low on the forehead to allow a bicoronal skin incision. A stereotactic planning MRI study was performed on a 1.5-T MR scanner (Signa LX, GE Healthcare). In the operating room, the propofol anesthesia was replaced by remifentanil infusion combined with Sevoflurane inhalation anesthesia. The propofol anesthesia was reintitiated for postoperative CT scanning (LightSpeed VCT, GE Healthcare). After CT scanning, the propofol infusion was stopped and the patient was extubated and then transferred to the recovery room.

Stereotactic Targeting. Anatomical targets were defined with the help of postmortem normal human brain materials stained with Nissl stain and anticholinesterase immunohistochemistry (E. J. Muñson, personal communication) combined with stereotactic atlas coordinates (Fig. 2). In the first cohort of 3 patients, the center of the nucleus basalis of Meynert (Ch4) was targeted bilaterally with separate implants (2 implants per patient) using the atlas coordinates x = 13 mm (lateral to the midline), y = 4 mm (posterior to the center of the anterior commissure), and z = −6 mm (below the intercommissural line). The target point was then adjusted based on individual anatomical variation. The tip of each implant was positioned at a z value 2 mm superior to the CSF space formed by the roof of the suprapontic cistern. The second cohort of 3 patients received a total of 4 implants, 2 of which were positioned as in the first cohort and another 2 implants that were positioned with their tips in the more anteromedial cholinergic basal forebrain containing the vertical limb of the diagonal band of Broca (Ch2). The corresponding atlas targets were determined to be x = 3 mm, y = 2–3
mm (anterior to the center of the anterior commissure), and $z = -3$ mm (below the intercommissural line). Again, the $z$ value was determined to position the implant tip 2 mm superior to the roof of the underlying CSF space. The trajectories to all targets were angled with respect to the entry point 20 mm anterior to the coronary suture and 30–50 mm lateral to the midline through a gyrus of the frontal lobe, while avoiding traversing any sulci, the horn of the lateral ventricle medially, and the insula laterally. The stereotactic coordinates were manually calculated at the MRI console (GE Healthcare) and verified using Leksell SurgiPlan (Elekta). Leksell SurgiPlan was also used to calculate the entry points and trajectories for implantation. Postoperatively, the positions of the barium-impregnated tethers (but not the active tip) were visualized using CT scanning. These images were merged with the stereotactic MR images by using neurosurgical operative planning software, iPlan 2.6 Cranial (BrainLAB). The positions of the probe tips, as calculated from the CT study, were compared with the coordinates obtained from the stereotactic MR images.

**Stereotactic Implantation.** With the patient in a supine semisitting position on the operating room table, the Leksell frame was attached to the operating table using a Mayfield adapter. To minimize CSF leakage and accumulation of intracranial air, the head of the patient was placed with the bur hole areas at the apex. The hair was minimally shaved in preparation for a linear bicoronal incision.

Entry points were marked according to the SurgiPlan coordinates, and a 14-mm bur (Medtronic, Inc.) was used to perforate the skull. The dura mater was coagulated with bipolar forceps and incised in a cruciate manner.

For histopathological diagnosis a cortical sample was obtained through one of the bur holes using small Nicola biopsy forceps.

A custom-made frame adapter (NsGene A/S) was attached to the arch of the Leksell stereotactic frame and used for the implantation of the ECB device (Fig. 1). The stereotactic coordinates were set on the Leksell frame, and the stereotactic needle was gently advanced to the target. At the target, the mandrel was removed and the NsG0202 implant was inserted into the target by using the frame adapter. The tether of the implant was secured to the wall of the bur hole using a purse-string nonabsorbable suture, and excess tether was cut. The bur hole was sealed with a piece of collagen sponge (Surgicel, Johnson & Johnson; Gelfoam, Pfizer, Inc.) and covered with a titanium plate 17 mm in diameter (bur hole cover, 1.6 mm, and PlusDrive cranial screws, 3 mm; both Synthes Corp.).

**Postoperative Patient Care and Monitoring**

Patients were monitored on the neurosurgical ward for 2–3 days postoperatively, followed by 3–6 days of inpatient care in a geriatric ward prior to discharge. Over the 12-month study period, patients were carefully monitored with a total of 13 scheduled visits or phone calls. Vital signs, concomitant medications, and adverse events were recorded at every visit. Sampling of CSF via lumbar puncture and cranial MRI, electroencephalography, and PET studies were performed at baseline and at 3 and 12 months postimplantation (further details are in press²).

**Surgical Implant Retrieval and Processing**

Twelve months after implantation, the NsG0202 de-
vices were explanted in all patients while under general anesthesia. The old scar was incised, and the titanium plates were removed. The tether was freed from surrounding bone using a rongeur. We retrieved the implants by gently pulling on the tether. The bur holes were sealed with Surgicel and a Gelfoam sponge. The titanium plates were not reattached.

The tethers of retrieved implants were cut, the cell-containing tips were placed in 1 ml of human endothelial serum-free medium (Invitrogen), and the NGF released was sampled as described above. Results were expressed in nanograms of NGF per 24 hours after extrapolation. For evaluation of cell morphology, devices were subsequently fixed in a 4% formalin solution, dehydrated in a graded ethanol series, and embedded in historesin (Leica Microsystems). Sections (5 μm) were mounted on slides coated with poly-L-lysine and stained with H & E (Bie & Berntsen A/S).

Results

Encapsulated Cell Biodelivery Device Production

The NsG0202 devices were manufactured under good manufacturing practices. All devices passed sterility testing and showed no leakage of cells. Devices released NGF at an average of 1.7 ± 0.2 ng/24 hours. A 5-week shelf life and 3-day storage in a tamper-proof thermally insulated box at the study site were validated with respect to device viability and NGF output.

Stereotactic Planning and Accuracy

There was some variation between the target coordinates determined from the individual MRI data set and those obtained via the standard stereotactic coordinate calculation from the stereotactic atlas. For x and y coordinates the differences were minor, but to avoid penetration of the supraoptic cistern, the z coordinate of the lateral target was slightly more superior than suggested by the atlas in most cases.

To verify positions of the intended targets, the postoperative CT scans were fused with the stereotactic MR images. By calculating the tether tip’s location, the tip of the cell-containing active portion of the device could be extrapolated and visualized on the MR images. Separate entry points were required to obtain safe trajectories for each target (Fig. 2).

Surgical Implantation and Retrieval

The use of a bicoronal surgical skin flap was surgically convenient with good and aesthetic wound healing. By placing the incision approximately 2 cm behind the most posterior bur hole, direct wound contact with the entry points could be avoided. Five of the 6 cortical biopsy samples consisted of enough tissue to confirm the histopathological diagnosis of AD.2 The custom-made stereotactic frame adapter proved to be accurate and easy to use by neurosurgeons experienced in stereotactic operative procedures. The total time—from the start of anesthesia induction, through preparation for MRI, target planning, and the implantation procedure, to extubation in the recovery room following postoperative CT—averaged 7 hours.

The surgical procedure for device explantation was uncomplicated for all patients. The bicoronal scar was incised, and the titanium plates were readily exposed. Partial or total cancellous bony closure of the bur holes had occurred at all entry points, but the tethers were easily identified, and the holes could be reopened down to the dura by using rongeurs without damaging the implants. Devices were easily retrieved from the brain tissue without adherence or any signs of hemorrhage. The procedure typically lasted 1 hour. All patients recovered without any new symptoms or sequelae and were discharged from the hospital on the following day.

Device Function After Retrieval

Explanted devices retrieved after 12 months were physically intact and without evidence of degradation. As depicted in Fig. 3, devices retrieved from the first cohort secreted a mean NGF rate of 0.17 ng/24 hours, which was approximately 10-fold lower than the mean preimplantation value of 1.73 ng/24 hours. Trace amounts of NGF could be detected from 2 of the 12 devices in the second cohort. In the first cohort, areas of both healthy-appearing nucleated cells and degenerating cells were detected. In the second cohort, only degenerating cells were seen on histological analysis. Moreover, histological analysis revealed no evidence of calcification of the devices, and the semipermeable membrane and polyvinyl alcohol foam were intact.

Clinical Safety and Tolerability

On the immediate postoperative CTs, no hemorrhage was detected in any of the patients. Small amounts of bifrontal intracranial air without mass effect were found in all patients. The most common adverse event was mild to moderate postoperative headache, most likely related to residual intracranial air. All patients could be mobilized the day after surgery. Neither of the 2 reported serious adverse events were deemed related to the device or the surgical procedures.2 Magnetic resonance images obtained at 3 and 12 months postoperatively showed that the implants remained in their original positions.

Discussion

The ECB technology represents a new restorative neurosurgery platform that can be applied to the targeted delivery of potent therapeutic and potentially regenerative factors to discrete anatomical areas of the brain. We chose AD as a relevant pathology for the local administration of NGF, as this molecule has shown therapeutic neurotrophic effects on the basal forebrain cholinergic system in multiple animal models of AD and because it has demonstrated potentially beneficial biological effects in 2 clinical pilot studies of NGF delivery in patients with AD: 1 with infusion and 1 with ex vivo gene therapy.2,18

Evidence in the literature suggests that the NGF signaling in AD is impaired and that the retrograde trans-
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Fig. 3. Bar graph (upper) showing NGF production before device implantation and after its explantation. Prior to implantation, the NsG0202 devices secreted 1.73 ng/24 hours of NGF on average. Following device explantation at 12 months, the secretion was reduced 10-fold to an average level of 0.17 ng/24 hours in the first cohort of patients. In the second cohort, trace amounts of NGF could be detected from 2 of 12 devices. Micrograph (lower) showing nucleated and viable cell clusters attached to the polyvinyl alcohol scaffold in an implant retrieved from the first cohort of patients. The larger cell cluster abuts the inside wall of the hollow fiber (bright structure). Original magnification × 200.

The primary objective of this study was to evaluate the safety and feasibility of stereotactic targeting of the cholinergic basal forebrain and determine the long-term tolerability and function of the NsG0202 implants in patients with AD. This is the first time that encapsulated cells have been placed directly in the human brain and the first clinical trial of NGF delivered by encapsulated cell implants. By implanting the devices in the brain parenchyma, we hoped to avoid the serious side effects of induced neuropathic pain reported in previous studies.2 10,19,20 Prior to this clinical study, NsG0202 devices were safety tested in Göttingen mini-pigs for up to 12 months.6 Fjord-Larsen et al.5 showed that devices implanted in the pig brain survived well and delivered NGF for at least 12 months. Therefore, it was unanticipated that device viability and NGF output after 12 months in the brains of humans with AD would be lower than in the pig model. However, NGF release was detected from all devices at explantation in the first group of 3 patients, the basal nucleus of Meynert (Ch4) was targeted, as this nucleus contains most of the cholinergic cell bodies (approximately 200,000/side) that project to cortical targets and the amygdala. This site was also the target in a previous clinical study.18 Since memory impairment is an early symptom in AD and the hippocampus is affected by large numbers of plaques and tangles, we also targeted the nucleus of the vertical limb of the diagonal band of Broca (Ch2) to administer NGF to the cholinergic projections to the hippocampal areas in the second cohort of patients.

Both precision and safety could be achieved with the stereotactic implantation of up to 4 implants per patient during 1 surgical procedure. Before starting this study, we anticipated that the implantation of multiple devices combined with a relatively long time under general anesthesia would increase the risk for postoperative confusion or other complications in patients with AD. However, this was avoided by applying a customized anesthesia protocol with careful monitoring of vital signs during the entire procedure.

The delivered daily dose of NGF was intentionally low in this initial safety study. Nonetheless, the NGF secretion was at a level anticipated to yield therapeutic effects, as experimental devices tested in the rat striatum positively affected the size of surrounding normal cholinergic neurons.5 Even though NGF secretion in the current study was relatively low, rodent7 and new pig studies (Fjord-Larsen et al., unpublished data) have shown that the combined diffusion from 2 NsG0202 implants, secreting 5 times the amount released by the implants in the present study, covers a volume of approximately 15 × 6 × 8 mm, indicating that most of the cholinergic basal forebrain in humans would be reached with 2 implants placed bilaterally. In addition, the NsG0202 implants released similar levels of NGF previously shown to be effective in animal models with cholinergic dysfunction.6 10,19,20 Prior to the cholinergic projections to the hippocampal areas in the first cohort, and histologically viable cells were demonstrated (Fig. 3), indicating that NGF had been delivered to these patients during the entire 12 months of the study. Given that trace amounts of NGF were detected from 2 additional devices in the second cohort and that degenerating cells were present in all devices after 12 months, it is likely that NGF was delivered over an extended time period in the second cohort of patients. These results indicate that either the human brain in AD is a more hostile milieu to the encapsulated cells than the young mini-pig brain, despite the fact that the latter represents a xenoge-
neic condition or that the device performance and handling differed between the 2 studies. To address these issues, an investigation is ongoing to determine if there are detrimental factors in the CSF of patients with AD that may affect the survival of the retinal pigment epithelial cell line. In addition, a new cell line has been made using a transposon-based gene expression system,2 and both the device scaffolding and the implantation procedure have been optimized to increase NGF secretion and improve cell viability. This second-generation implant is currently being evaluated in a recently initiated dose escalation study in 4 patients. With several months of optimized NGF secretion, it is anticipated that the treatment could change the slope of degeneration and yield a long-lasting significant therapeutic effect.

Conclusions

In this first clinical study, we accomplished the major goals of demonstrating the implantability, retrievability, 12-month NGF secretion, long-term safety, and tolerability of NsG0202 implants in patients with AD. Even in a condition with extensive brain atrophy, multiple deep-seated targets could be accurately and safely reached. With some revisions, this restorative neurosurgical technology platform warrants additional testing in AD and in other relevant neurological disorders, such as Parkinson and Huntington disease, in which the targeted delivery of regenerative proteins could be beneficial. With additional development, the technology is likely to become a new therapeutic tool in functional and restorative neurosurgery that combines the advantages of gene therapy with the simplicity and safety of an implantable and retrievable device.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Wahlberg, Lind, Almqvist, Tornøe, Selldén, Seiger, Eriksdotter-Jönhagen, Linderoth. Acquisition of data: Wahlberg, Lind, Almqvist, Kusk, Tornøe, Juliusson, Söderman, Selldén, Eriksdotter-Jönhagen, Linderoth. Analysis and interpretation of data: Wahlberg, Lind, Almqvist, Kusk, Seiger, Eriksdotter-Jönhagen, Linderoth. Drafting the article: Wahlberg, Lind, Almqvist, Linderoth. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wahlberg. Statistical analysis: Kusk, Eriksdotter-Jönhagen. Administrative/technical/material support: Wahlberg, Lind, Almqvist, Tornøe, Juliusson, Seiger, Eriksdotter-Jönhagen, Linderoth. Study supervision: Wahlberg, Lind, Almqvist, Seiger, Eriksdotter-Jönhagen, Linderoth. Supervised production and NGF analysis: Kusk. Generated cell line and device design and instrumentation: Tornøe. Quality assurance, regulatory strategy, and implementation of production and study: Juliusson. Targeting and neuroradiology protocols: Söderman. Designed anesthesia protocols and implementation: Selldén.

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Address correspondence to: Lars U. Wahlberg, M.D., Ph.D., NsGene, Inc., 225 Chapman Street, Providence, Rhode Island 02905. email: luw@nsgene.com.